ARCHIVES of INTERNAL MEDICINE

VOLUME 61 MARCH 1938 NUMBER 3

COPYRIGHT, 1938, BY THE AMERICAN MEDICAL ASSOCIATION

RELIEF OF DIABETIC PAIN OF NEUROCIRCULATORY ORIGIN BY ORAL ADMINISTRATION OF SODIUM CHLORIDE

H. R. SANDSTEAD, M.D.

Assistant Surgeon, United States Public Health Service

WASHINGTON, D. C.

AND

A. J. BEAMS, M.D.

Consultant in Internal Medicine, United States Marine Hospital

CLEVELAND

In a previous paper one of us [1] presented certain observations indicating that the pain of diabetic neuritis was relieved temporarily by the oral administration of sodium chloride in amounts ranging from 15 to 90 Gm. daily over periods of two to four weeks with interruptions of ten to fourteen days. It appeared likely that the relief thus obtained was due to a vasodilating effect of the sodium chloride. The present study was undertaken primarily for the purpose of studying the effect of this salt on a larger series of diabetic patients complaining of pain who had not been relieved by the usual diabetic management.

METHOD

Thirteen patients with pain of either neuritic or vascular origin were studied. For the purpose of study the patients were divided into three groups: first, a group of seven patients in whom definite neurologic signs were found, consisting of hyporeflexia, areflexia and sensory changes; second, a group of three patients whose chief symptoms were severe arteriosclerosis and its sequelae; third, a group of three patients in whom objective neurologic signs were not found and whose arteriosclerosis would not ordinarily be considered significant.

All these patients were observed for a control period of two weeks or longer. Eight of them were purposely given an inadequate amount of insulin in order to permit observation of the effect of sodium chloride on the level of the blood sugar. The remaining five patients were given a sufficient amount of insulin to maintain a satisfactory blood sugar level.

A determination of the blood sugar level was made twice weekly during fasting and at 11 a. m. and at 2: 30 p. m. at least once weekly in all cases except for two outpatients, for whom three determinations were made at intervals of about two weeks. The other laboratory procedures included determinations of the values for serum calcium, blood chloride, plasma cholesterol and urinary chloride.

1. Sandstead, H. R.: The Effects of the Oral Administration of Sodium Chloride in Diabetes, Hosp. News **3**:21 (Nov. 1) 1936.

renal function tests, Wassermann tests of the blood and the usual examinations of the blood and urine made as a routine.

The cutaneous histamine reaction, as described by de Takáts,[2] was tested in seven of the patients before and after the administration of salt. Roentgen examinations of the legs were made as a routine to determine whether calcification of the arteries was present.

The same method of administration of the salt was used as in the previous study.[1] Briefly, it was as follows: The salt was given in solution three or four times daily and was sipped over a period of half an hour. The dose given daily was 0.25 to 0.5 Gm. per kilogram of body weight. This was found to be the maximum dose not causing any gastric disturbance. In order to relieve the monotony of taking the salt and to prevent possible untoward effects, the salt was given for interrupted periods of two to four weeks over periods ranging from one to twelve months.

OBSERVATIONS

Group 1: Patients in Whom Definite Neurologic Signs Were Found.—In this group of seven patients there were five who could be classed as having severe diabetes and two who could be classed as having mild diabetes. The ages ranged from 37 to 65 years, and the known duration of the diabetes was from two and one-half to twelve years. All the patients had peripheral neuritis. In four the symptoms appeared at the onset of the diabetes, and in three they appeared one and one-half to six years after the onset. All continued to have neuritic pain in spite of the treatment for diabetes. The chief symptoms were pain, hyperesthesia and muscular weakness. The objective neurologic signs consisted of absence of the achilles tendon reflexes in all the patients, absence or diminution of the knee jerks in six, absence of the reflexes in the upper extremities of three and absence of the vibratory sense in the lower extremities of two. The site of the neuritis was limited to the lower extremities in five patients, in one patient the neuritis involved the entire body and in one it involved both upper and lower extremities. Vascular disease was present to some degree in all the patients, as noted in table 1. The degree of arteriosclerosis was determined by palpation of the peripheral arteries, ophthalmoscopic and roentgen examinations and histamine tests. There were four patients in this group who showed calcification of the peripheral arteries roentgenographically and four without pulsation of the dorsalis pedis arteries.

The patients in this group have been under observation for two and one-half to twenty-four months and have received sodium chloride orally over interrupted periods of one and one-half to twelve months. Three of the patients obtained complete relief from pain, and four obtained marked relief. There was definite improvement in the circulation of three on

2. de Takáts, G.: The Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**:769 (Nov.) 1931.

whom the cutaneous histamine test was performed, as shown by the increase in the response, and in two of four patients evidence of improvement was shown by the return of the pulsations of the dorsalis pedis arteries. No changes were observed in the objective neurologic signs after the administration of salt.

The case of B. J., a woman with neuritis of nine years' duration, is of particular interest in that she has been treated as an outpatient, receiving orally 20 to 24 Gm. of sodium chloride for interrupted periods of two to three weeks for the past

TABLE 1.—*The Effect of the Oral Administration of Sodium Chloride on Neuritic Patients with Definite Neurologic Signs* *

		Control Period								Period of Administration of Salt			
Patient	Age, Years	Duration of Diabetes, Years	Duration of Pain, Yr.	Diabetes	Pain	Degree of Arteriosclerosis	Average Blood Sugar Value (Fasting), Mg. per 100 Cc.	Units of Insulin Daily	Histamine Test Before Administration of Salt	Sodium Chloride, Gm. Daily	Length of Time Salt Was Administered, Mo.	Histamine Test After Administration of Salt	Relief of Pain
W. C.	47	2½	1	Severe	Severe	3	140	40	1	20	1½	2	Marked
S. G.	40	2½	2½	Moderate	Severe	2	195	20	1	28	3	3	Complete
W. L.	37	5	5	Severe	Severe	2	367	70	..	11 to 16	5	..	Marked
B. J.	44	12	9	Severe	Severe	3	339	60	1	20 to 40	4	3	Marked in hands; complete in lower extremities
A. R.	65	5	5	Severe	Moderate	4	256	65	..	20	4	..	Marked
E. H.	38	2½	2½	Severe	Moderate	2	245	124	..	60 to 30	12	..	Complete
W. M.	60	8	2	Moderate	Severe	4	248	0	..	30 to 16	6	..	Complete

* In tables 1 to 3 the degree of arteriosclerosis is designated as follows: 1 indicates mild; 2, moderate; 3, moderate, with roentgen evidence of calcification in the vessels of the legs, and 4, severe, as shown by extensive calcification. The response to the cutaneous histamine test is shown as follows: 0 indicates no response; 1, faint; 2, fair, and 3, marked reactions.

four months. Progressive improvement in the relief of pain has been obtained during the past three months. This is the first time in nine years that she has been completely free from pain in the lower extremities, and for the first time in several winters she has not required extra protection of the feet at night for warmth. There has also been considerable relief of pain in the hands. The pulsations of the dorsalis pedis arteries are again palpable.

The following case report illustrates the effect of salt on neuritic pains which had caused complete disability.

W. C., a man aged 47 years with diabetes of two and one-half years' duration, was admitted to the hospital on Dec. 11, 1936, because of burning pain over the

entire body, most marked in the feet and legs, weakness, loss of weight and poor appetite. Neuritic symptoms had appeared about one year before and had become progressively more severe. He had been on a diet containing 235 Gm. of carbohydrate, 77 Gm. of protein and 90 Gm. of fat and had been taking a total of 78 units of insulin daily.

Examination revealed a poorly nourished man, weighing 103 pounds (47 Kg.). There was arteriosclerosis of grade 3. The dorsalis pedis and posterior tibial arteries could not be palpated. There was hyperesthesia over the entire body; it was so marked in the lower extremities that the patient could not tolerate the touch of bedclothes. The only other neurologic finding was absence of the achilles tendon reflexes. During the control period he was on a diet containing 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat and received a total of 40 units of insulin daily. The blood sugar value was maintained at an average fasting level of 140 mg. Although the diabetes was well controlled, it was necessary for him to remain in bed on account of the neuritic symptoms.

The period of interrupted oral administration of salt began on Jan. 6, 1937. He was given 20 Gm. daily for the remainder of the month. The dosage of insulin was not changed, and the diet was increased without elevation of the blood sugar level. By the end of this period the pains were minimal. Administration of salt was resumed on February 15 and was continued until March 1, at which time the patient had only an occasional pain. He had gained 7 pounds (3 Kg.), there was less weakness and he was active about the ward. The diet had been increased to 200 Gm. of carbohydrate, 76 Gm. of protein and 86 Gm. of fat, without changing the dosage of insulin, and the blood sugar level was not elevated.

Before admission to the hospital this patient had been receiving an adequate diet, and the diabetes had been controlled with large doses of insulin. During the initial period after his admission to the hospital the blood sugar level was maintained at 140 mg. However, during this time he obtained no relief from the neuritic symptoms. It was only after the administration of sodium chloride that these symptoms disappeared. This is good evidence that neither hyperglycemia nor vitamin deficiency was responsible for the neuritis.

What was true in this case was true for the entire group. After the administration of sodium chloride it was possible to increase the diet and to reduce the dosage of insulin and at the same time to maintain the blood sugar level or reduce it for all the patients except one, whose insulin requirement was increased with the increase in diet. It appeared at first that the increase in diet might be a factor in relieving the neuritic symptoms, but there was no constant relation between the improvement of the symptoms and the increase in diet.

Group 2: Patients with Severe Arteriosclerosis.—Three patients are included in this group (table 2). All of them had severe arteriosclerosis without objective neurologic changes. Their diabetes was easily controlled with small amounts of insulin. In each instance the diet was increased, and the dosage of insulin was reduced when salt was given.

F. H. K. had had an amputation of the left leg for gangrene one year prior to the present admission to the hospital and had a painful, cold, cyanotic foot. After six months of interrupted administration of salt the pains were completely relieved, the foot was warm and its color was good.

C. S. had had an amputation for gangrene several months before the present admission to the hospital. The remaining leg was cold and moderately painful. After the administration of 18 Gm. of salt daily for twenty days the leg was warm and the pains had disappeared. Three weeks after discontinuance of the salt therapy he died as the result of a mycotic aneurysm of the left femoral artery and myocardial infarction.

The following case is reported in detail because it shows the remarkable effect that sodium chloride had on the course of the disease.

M. F., a man aged 66 years with diabetes of four years' duration, was admitted on May 18, 1936, because of deep burning and cramping pain of the feet and legs which had been present for about three years. He had not been on a rigid diet and was taking 20 units of insulin daily. He had glaucoma six months before entry into the hospital.

TABLE 2.—*The Effect of the Oral Administration of Sodium Chloride on Diabetic Patients with Pains of Arteriosclerotic Origin*

		Control Period								Period of Administration of Salt			
Patient	Age, Years	Duration of Diabetes, Years	Duration of Pain, Yr.	Diabetes	Pain	Degree of Arteriosclerosis	Average Blood Sugar Value (Fasting) Mg. per 100 Cc.	Units of Insulin Daily	Histamine Test Before Administration of Salt	Sodium Chloride, Gm. Daily	Length of Time Salt Was Administered	Histamine Test After Administration of Salt	Relief of Pain
C. S.	68	19	4	Moderate	Moderate	4	142	15	2	18	20 da.	3	Complete
F. H. K.	65	4	2	Moderate	Severe	4	253	40	1	14	6 mo.	3	Complete
M. F.	66	3	3	Moderate	Severe	4	153	15	0	42 to 21	5 mo.	2	Complete

Examination revealed a moderately obese elderly man, weighing 213 pounds (96.6 Kg.), who appeared chronically ill. The essential findings were arteriosclerosis of grade 4, absence of pulsation in the dorsalis pedis and posterior tibial arteries and moderate hypertrophy of the left ventricle. There was choroidal and retinal arteriolar sclerosis of grade 3, with numerous small hemorrhages disseminated over the fundi. There was a negative response to the histamine flare test on the knees.

For a control period of two weeks he was placed on a diet containing 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat, with 15 units of insulin daily, without improvement of the pain. During this period the blood sugar was maintained at a satisfactory level. The use of insulin was discontinued, and the patient was given 42 Gm. of sodium chloride daily the first two weeks, 21 Gm. daily the third week and 42 Gm. daily during the fourth week. During this period the blood sugar was maintained at approximately the same level as during the control period. Three weeks after the administration of sodium chloride was started the pains in the legs were much relieved, and the patient was taking short

walks. After a rest period of two weeks he was again given 21 Gm. of salt daily for two weeks. He was completely relieved of the pain in the legs and feet by the end of this period.

Histamine flare tests on July 13 showed a fair response. During this period there was a recurrence of glaucoma in each eye. Operations for relief of this condition were unsuccessful. He was not given sodium chloride again for four months. Two months after discontinuing the use of sodium chloride he again complained of increasing pain in the feet. One month later large bullae appeared on the great toes, there was an indolent ulcer on the heel of the left foot and the pains in the legs were severe. The ulcer increased to 2 by 2 cm. in diameter, and the distal third of the affected toes became black. He was again given 21 Gm. of sodium chloride daily for three weeks. By the end of this period the necrotic crust had sloughed, and epithelization was nearly complete. The ulcer showed signs of healing, and the pains were minimal. Treatment with sodium chloride was discontinued because of slight edema of the ankles. After a three weeks' rest period he was again started on 21 Gm. of salt, and this was continued for two weeks. By the end of this period the lesions were completely healed, the pulsations of the dorsalis pedis arteries were palpable and he was free from pain.

The relief of symptoms and the improvement in the circulatory changes after the administration of sodium chloride in this group of patients are striking. All of them obtained complete relief from pain and definite improvement in the circulation, as shown by the change in color and the increase in temperature of the feet and by the response to the histamine test.

Group 3: Patients with Neuritic Pains in Whom Neurologic Signs Were Not Found.—Three patients are included in this group (table 3).

O. R., whose pain was mild, may have been relieved by control of the diabetes. However, this patient had been taking 70 units of insulin while on a diet containing 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat. After several months of interrupted administration of sodium chloride the pains were completely relieved, the dosage of insulin was reduced to 35 units daily and the diet was increased to 200 Gm. of carbohydrate, 70 Gm. of protein and 200 Gm. of fat.

R. M., whose diabetes was under good control without improvement in the pain during the preliminary period, was completely relieved one month after the administration of salt was started. The dosage of insulin was reduced in this instance from 55 to 38 units, the diet remaining unchanged. Two months after discharge he reported that the pains had not returned.

The following case is reported in detail because it shows that some factor other than hyperglycemia is responsible for pain.

L. H., a man aged 41, with diabetes of fourteen years' duration, was admitted to the hospital on Dec. 3, 1936, complaining of drowsiness, pain over the entire body but most marked in the feet, legs and arms, and loss of weight and strength. The neuritic symptoms were of about eight months' duration. He had been in diabetic coma nine times in the past six months. He had not been rigidly following a diet, and he was taking 24 units of insulin daily.

Examination revealed a moderately undernourished man, weighing 136½ pounds (62 Kg.), with acidosis. The remainder of the physical examination disclosed nothing of importance except mild arteriosclerosis.

During the control period he was on a diet containing 150 Gm. of carbohydrate, 70 Gm. of protein and 80 Gm. of fat, with a total of 40 units of insulin daily. The acidosis disappeared within a few days, but the blood sugar level remained elevated, averaging 329 mg. during fasting. The initial period of interrupted oral administration of salt began on December 18 and continued until Jan. 2, 1937, 30 Gm. being given daily. The average blood sugar value during fasting was reduced by 65 mg. during the period, without change in the dosage of insulin. He stated that the pains had diminished slightly. After the discontinuance of treatment with sodium chloride the blood sugar returned to the previous level in spite of an increase in the dosage of insulin by 10 units. The second period of administration of salt was begun on January 13 and continued until January 25, 20 Gm. being given daily. During this period the diet was increased to 175 Gm. of carbohydrate, 76 Gm. of protein and 106 Gm. of fat. During fasting the blood sugar value averaged 304 mg. The hyperglycemia may be explained in part by

TABLE 3.—*The Effect of the Oral Administration of Salt on Neuritic Patients Without Objective Neurologic Signs*

		Control Period								Period of Administration of Salt			
Patient	Age, Years	Duration of Diabetes	Duration of Pain, Mo.	Diabetes	Pain	Degree of Arteriosclerosis	Average Blood Sugar Value (Fasting), Mg. per 100 Cc.	Units of Insulin Daily	Response to Histamine Before Administration of Salt	Sodium Chloride, Gm. Daily	Length of Time Salt Was Administered	Response to Histamine After Administration of Salt	Relief of Pain
O. R.	34	14 mo.	14	Severe	Mild	1	252	70	..	26	3 mo.	..	Complete
L. H.	41	14 yr.	8	Severe	Severe	1	329	40	2	30 to 20	5 wk.	3	Complete
R. M.	46	11 yr.	2	Moderate	Severe	2	164	55	..	30	1 mo.	..	Complete

acute nasopharyngitis. The pain gradually disappeared, and by the end of the period he had only an occasional shooting pain in the legs.

After discontinuance of treatment with salt he was given a long "rest period," which lasted until March 11. During this period the diet was increased to 200 Gm. of carbohydrate, 76 Gm. of protein and 106 Gm. of fat. The dosage of insulin was increased to 60 units daily in order to keep the blood sugar at a satisfactory level. The pains increased and were as severe as when he was admitted to the hospital. The administration of sodium chloride was resumed on March 11 at his request and was continued for the remainder of the month. During this period he received 20 Gm. daily, and the dosage of insulin was reduced by 10 units. The blood sugar level was not elevated above that of the previous month, and the patient was completely relieved of pain.

When this patient was admitted to the hospital he was in diabetic acidosis; therefore, dehydration must be considered as a factor in producing the neuritic pains. However, after he was given sufficient fluids and the acidosis had disappeared he continued to have the neuritic symptoms, which were relieved with sodium chloride. While he was taking sodium chloride, the pains ceased even though the blood sugar level

was elevated, and when it was discontinued the pains returned in spite of a satisfactory blood sugar level. Hyperglycemia appeared not to be a factor in causing the neuritic pains.

COMMENT

We have presented observations on thirteen diabetic patients with pains which may be classed as of neuritic origin in ten (groups 1 and 3) and of vascular origin in three. The pains in most of the cases had been of long duration and had persisted in spite of treatment for the diabetes. All the patients received marked to complete relief of the pains after oral administration of sodium chloride. The patients with severe arteriosclerosis showed, in addition to the relief of pain, definite signs of improvement in the vascular disease, as evidenced by the healing of gangrenous toes and of an indolent ulcer and by changes in the color and temperature of the feet. In the group of patients with neuritic pains the only change noted in addition to the relief of pain was the increase in response to the histamine test, indicating improvement in the circulation after administration of sodium chloride. In these two groups the relief of pain appeared to be accompanied with signs of improvement in the circulation. This suggests that ischemia, the result of vascular disease, may be the cause of the neuritic symptoms.

This study raises the question as to the possible etiology of diabetic neuritis, which has long been a subject of considerable controversy. Jordan [3] has made an extensive review of the literature and has reported his observations on a group of two hundred and twenty-six patients with diabetic neuritis. He placed his patients in four groups, according to whether they had hyperglycemic, circulatory, degenerative or neuritic disorders. Those with hyperglycemia presented no factor except hyperglycemia to explain the neuritis. Only thirty-four patients were placed in this group. Over 95 per cent of the patients in the other groups had evidence of vascular disease, which, he pointed out, may be a factor in causing the neuritis.

It has already been mentioned that neither hyperglycemia nor vitamin deficiency appeared to be responsible for the neuritic symptoms of any of our patients. Foci of infection were found in a few instances; however, no treatment was given for these conditions until after relief of the neuritis had been obtained with sodium chloride. There were no other possible causes of neuritis found, such as anemia, metal poisoning or alcoholism. The Wassermann reaction of the blood was negative in all the cases, and there was no clinical evidence of syphilis to explain the neurologic findings.

---

3. Jordan, W. R.: Neuritic Manifestations in Diabetes Mellitus, Arch. Int. Med. **57**:307 (Feb.) 1936.

We have not studied a sufficient number of cases to draw any definite conclusions, but the fact that both the patients with neuritic pain and those with severe arteriosclerosis obtained relief from pain, accompanied with signs of improvement in the circulation, is evidence that ischemia, the result of vascular disease, primarily arteriosclerosis, is the probable cause of the neuritic symptoms. This view is in agreement with that of Woltman and Wilder,[4] who, in a comprehensive study of this problem, have pointed out that neuritis commonly occurs in patients whose diabetes is under control, that is, in patients who are free from either acidosis or glycosuria. They reported ten cases of neuritis in which autopsy showed a certain amount of arteriosclerosis of the intraneural vessels. This they considered consistent with the idea of ischemia of the nerves as a factor in the neuropathy.

The improvement observed in the vascular disease of our patients after the oral administration of sodium chloride is in accord with the observations of Perlow,[5] who found that certain types of vascular disease in nondiabetic patients were benefited by treatment with hypertonic solution of sodium chloride intravenously, and also those of de Takáts,[6] who has recommended the oral administration of sodium chloride for occlusive vascular disease.

In view of our findings and those just cited it seems that the oral administration of sodium chloride is rational therapy for the neurocirculatory complications of diabetes.

We are not able to offer an explanation for the action of sodium chloride in producing the circulatory changes which have been observed in patients with vascular disease. The chemical studies of the blood, which included analyses of the chloride, calcium and cholesterol contents, did not show any change after the administration of sodium chloride. The determinations of the chloride content of the urine showed the output of chloride to be increased in proportion to the amount given. Only two of the patients showed slight edema of the lower extremities, and no constant change was noted in the weight as a result of the administration of salt. No impairment of renal function was found after the administration of sodium chloride, nor was there evidence of any other ill effects.

4. Woltman, H. W., and Wilder, R. M.: Diabetes Mellitus: Pathologic Changes in the Spinal Cord and Peripheral Nerves, Arch. Int. Med. **44**:576 (Oct.) 1929.

5. Perlow, S.: Conservative Treatment in Occlusive Vascular Diseases of the Extremities, Ann. Int. Med. **8**:741 (Dec.) 1934.

6. de Takáts, G.: Peripheral Vascular Disease: Its Significance for General Practitioners and Specialists, J. A. M. A. **104**:1463 (April 27) 1935.

SUMMARY AND CONCLUSIONS

Observations have been made, before and after the oral administration of sodium chloride, on thirteen diabetic patients, with pain of neuritic origin in ten and with pain of arteriosclerotic origin in three.

All the patients obtained complete or marked relief of the neuritic symptoms after the administration of sodium chloride.

The relief of pain was accompanied with signs of improvement in the vascular disease in the patients with arteriosclerotic pain and with improvement in the circulation of those with neuritic pain, as shown by the histamine test.

The observations made in this study indicate that ischemia, the result of vascular disease, primarily arteriosclerosis, is responsible for the neuritic symptoms.

In view of our findings the oral administration of sodium chloride appears to be the rational treatment for the neurocirculatory complications of diabetes.

The members of the staffs of the Cleveland City, Lakeside, St. Alexis and St. Luke's hospitals cooperated in furnishing us patients for this study.

ELECTROCARDIOGRAPHIC PATTERNS IN ACUTE PERICARDITIS

EVOLUTION, CAUSES AND DIAGNOSTIC SIGNIFICANCE OF PATTERNS IN LIMB AND CHEST LEADS; A STUDY OF FIFTY-SEVEN CASES

SAMUEL BELLET, M.D
AND
THOMAS M. McMILLAN, M.D.
PHILADELPHIA

From time to time various changes have been shown to develop in the electrocardiograms of patients with acute pericarditis.[1] Often these have been striking, consisting in the main of diminished amplitude of the ventricular complex in the presence of effusion, inversion of the T wave and elevation of the RST segment. In studying fifty-seven cases of acute pericarditis of different etiologic types we encountered changes of this type sufficiently often to lead us to feel that striking alterations of the electrocardiogram frequently develop in cases of acute pericardial disease and that in a certain percentage of cases they may assume a pattern that is distinctive enough to have diagnostic value. In the present paper we wish to describe these changes and to discuss their cause.

MATERIAL

The varieties of pericarditis represented in our series of fifty-seven cases were varied and included the following etiologic types: rheumatic pericarditis (thirteen cases), pneumococcic pericarditis (six cases), uremic pericarditis (five cases),

From the Division of Cardiology of the Philadelphia General Hospital and the Robinette Foundation for the Study of Cardiovascular Diseases of the University of Pennsylvania.

1. (*a*) Harvey, J., and Scott, W.: Changes in the Electrocardiogram in Course of Pericardial Effusion with Paracentesis and Pericardiotomy, Am. Heart J. **7**:532, 1932. (*b*) Oppenheimer, B. S., and Mann, H.: An Electrocardiographic Sign in Pericardial Effusion, Proc. Soc. Exper. Biol. & Med. **20**:431, 1923. (*c*) Porte, D., and Pardee, H. E. B.: The Occurrence of Coronary T Wave in Rheumatic Pericarditis, Am. Heart J. **4**:584, 1929. (*d*) Purks, W. K.: The Occurrence of a Coronary T Wave in Purulent Pericarditis, South. M. J. **24**: 1032, 1931. (*e*) Scherf, D.: Ein elektrokardiographisches Zeichen bei Erguss in Herzbeutel, Wien. klin. Wchnschr. **43**:298 (March 6) 1930. (*f*) Schwab, E. H., and Herrmann, G.: Alterations of the Electrocardiogram in Diseases of the Pericardium, Arch. Int. Med. **55**:917 (June) 1935. (*g*) Scott, R. W.; Feil, H., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion: Clinical, Am. Heart J. **5**:68, 1929.

hematopericardium (rupture of an aneurysm, one case; stab wound, two cases), neoplastic pericarditis (two cases), pericarditis due to staphylococcic septicemia (one case), tuberculous pericarditis (twenty cases) and pericarditis of unknown etiology (seven cases).

The clinical diagnosis was confirmed by necropsy in twenty-two cases, by surgical intervention in four cases and by paracentesis in four additional cases. In the remainder of the fifty-seven cases characteristic clinical and roentgen findings established the diagnosis, in our opinion, beyond reasonable doubt; these usually included the demonstration of a friction rub or the presence of a characteristic fluoroscopic silhouette.

ELECTROCARDIOGRAPHIC FINDINGS

The incidence of electrocardiographic changes was as follows: No alterations were seen in twelve cases; definite abnormalities were present in forty-five. We have considered as definite abnormalities unmistakable deviation of the RST segment in one or more limb or chest leads (twenty-six cases) and definite inversion of the T wave (nineteen cases). We also encountered a ventricular complex of low amplitude in seventeen of our fifty-seven cases and interesting types of auricular arrhythmia, including extrasystoles, flutter and fibrillation, in six additional cases. Because these abnormalities commonly occur in association with other forms of cardiac disturbances, we have not included them among the abnormal findings and shall not consider them further.

Deviation of the RST Segment.—Among previous observers, Schwab and Herrmann [11] alone made use of chest leads. They applied this method in only two cases and concluded that it furnished no information of differential diagnostic value. We used three chest leads [2] as well as three limb leads in all but five of the twenty-six cases listed in which there was deviation of the RST segment and found that their use frequently gives information of importance. Often they exaggerate deviation of the RST segment that is present but inconspicuous in limb leads, or they reveal deviation which is not shown in limb leads.

Alterations of the RST segment may be really striking, and in the combined limb and chest leads they may assume a pattern which we have not encountered in association with any condition but acute peri-

2. Throughout our studies the precordial leads were applied in the manner previously described (Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Further Observations on the Use of Direct Chest Leads in Coronary Occlusion, Arch. Int. Med. **52**:752 [Nov.] 1933). Lead IV was obtained by placing the right arm electrode over the cardiac apex and the left arm electrode at the angle of the left scapula. In lead V the right arm electrode was placed at the apex; the left leg electrode, on the customary site. In obtaining lead VI the left arm electrode was placed at the angle of the left scapula; the left leg electrode, in its normal position.

carditis. The important features of this pattern are: (1) elevation of the RST segment in leads I to III or in leads I and II alone; (2) depression of the RST segment in leads IV and V, with a well preserved initial downward deflection; (3) elevation of the RST segment in lead VI, even when there is no elevation in lead III.[3]

In our experience this combination of findings is not uncommon in cases of acute pericarditis. In twenty-one of the forty-five cases in which there were definite abnormalities this pattern was strictly complied with; in three additional cases in which direct leads were not used the indirect leads were characteristic.

The relative frequence of these characteristic findings indicates that they may possess some diagnostic importance; we have not so far encountered them exactly in association with any other condition, though we are not prepared to say that they may not so occur. In certain instances of occlusion of the anterior coronary artery the electrocardiographic findings are similar, but there are as a rule certain definite differences, which will be discussed later.

Alteration of the RST segment in cases of pericarditis is a transient and frequently brief phenomenon. We have never observed it to persist in the limb leads for more than twelve days. The detection of these changes, therefore, is not to be expected unless tracings are obtained frequently. The chest leads continued to show deviations for several days, as a rule, after they had disappeared from the limb leads.

Since deviations in the RST segment are of brief duration and since they do not disappear simultaneously [4] from individual leads, one can expect to encounter tracings in which perhaps striking changes were present in one or more limb or chest leads, with slight or no changes in the other leads (fig. 2 *A* and *C*). In three additional cases of our series these findings were noted. Although in such cases the pattern is not strictly complied with, these isolated changes if they are marked may still be suggestive of pericarditis and are therefore of some importance.

In some of our cases of pericarditis in which deviation in the RST segment was not noted either in the limb or in a conventionally placed precordial lead, we discovered that modifying the usual chest lead by placing the anterior electrode over the area of friction not infrequently revealed these alterations. In two cases of tuberculous pericarditis in which the electrocardiograms showed no deviation in the RST segment in either the limb or the customary precordial lead, definite

3. Elevation of the RST segment in all three leads may occur even in the presence of left axis deviation (fig. 5).

4. The deviations in the RST complex usually disappear first from the leads in which they are least marked in the initial tracing.

alterations were brought out by this maneuver. In four other cases deviation in the RST segment in the usual chest lead was definitely exaggerated when the electrode was placed over the area of friction (fig. 4).

Striking deviations in the RST segment were encountered in the electrocardiograms of patients with all the varieties of acute pericardial disease represented in our series (table 1). They develop most readily apparently in association with the pneumococcic type; they were infrequent in cases of the tuberculous variety. This difference in incidence will be discussed later.

TABLE 1.—*Electrocardiographic Changes Associated with Pericarditis* *

Etiologic Factor	Total Number of Cases	Deviation in RST Segment, Limb Leads		RST Segment in Precordial Leads						
		I to III	I and II	Depression IV and V	Elevation VI	Change in T Wave Only	Negative Findings	Died	Necropsy	Operation
Rheumatic pericarditis	13	5	3	7	6	2	3	3	1	1
Pneumococcic pericarditis	6	4	2	6	6	..	..	6	5	2
Uremic pericarditis	5	2	..	3	2	1	1	5	4	..
Hematopericardium	3	2	..	1	Not done	1	..	2	1	..
Neoplastic pericarditis	2	..	1	1	1	..	1	1	1	..
Pericarditis due to staphylococcic septicemia	1	..	1	Not done	Not done	..	..	1	1	..
Tuberculous pericarditis	20	1	1	1	1	12	5	12	7	1
Pericarditis of unknown origin	7	2	..	3	3	3	2	4	2	..
Total	57	16	8	22	19	19	12	34	22	4
		24								

* In three of the twenty-four cases in which there was deviation of the RST segment in the limb leads, no precordial lead was made; in one case there was no change in the precordial leads, and in three cases no deviation was observed in lead VI. In two additional cases a deviation in the RST segment was observed in the precordial and not in the limb leads.

Changes That Succeed Deviation of the RST Segment.—Since deviation of the RST segment is transient and of brief duration, the changes that succeed it are of interest. The usual development in the limb leads, as shown in fifteen cases, is a gradual return of the RST segment toward the base line. When this is nearly complete the upright T wave begins to show a dip downward in its terminal portion and finally becomes frankly inverted and usually cove-shaped. This may occur in all three leads if the RST segment is initially elevated in all leads; it involves leads I and II only when the RST segment is affected in only these leads. If recovery occurs, this configuration, after persisting for a variable time, may become entirely normal.

Occasionally the T wave of the indirect leads never becomes inverted, but assumes its normal configuration as the deviated RST segment returns to the iso-electric line. We observed this behavior in three cases.

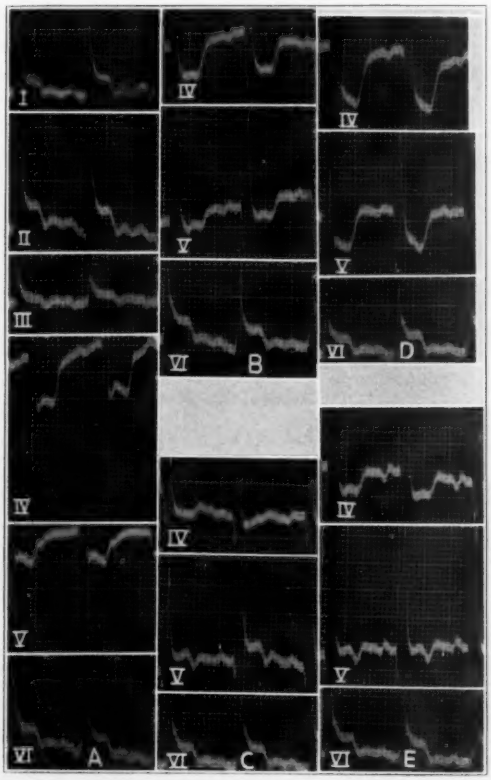


Fig. 1.—Electrocardiograms of a patient aged 48 with pneumococcic pericarditis. Postmortem examination revealed a purulent exudate, with little fluid present in the pericardial sac. Microscopic study revealed infiltration of the inflammatory process into the epicardial portion of the myocardium (fig. 8). All the tracings were made on Feb. 20, 1935. *A*, note the elevation of the RST segment in leads I to III and the marked depression, with preservation of the initial downward deflection, in leads IV and V, with elevation of the RST segment in lead VI. *B*, the anterior electrode was placed over the third interspace to the left of the sternum; *C*, over the base; *D*, over the lower portion of the sternum, and *E*, over the fifth interspace to the right of the sternum. Note that deviation of the RST segment is present in *B*, *C*, *D* and *E* and that the algebraic summation of the deviations of the RST segment in leads IV and VI is approximately equal to those of lead V.

In six of our cases a peculiar type of inversion of the T wave was noted in limb leads as an intermediate stage between the elevated RST and the common type of inverted T wave. Taking origin at or slightly above the iso-electric line, the gradual more or less normal upstroke of the T wave is followed by a sharp, beakline downward dip, which inverts the terminal portion of the T wave. The T waves which are

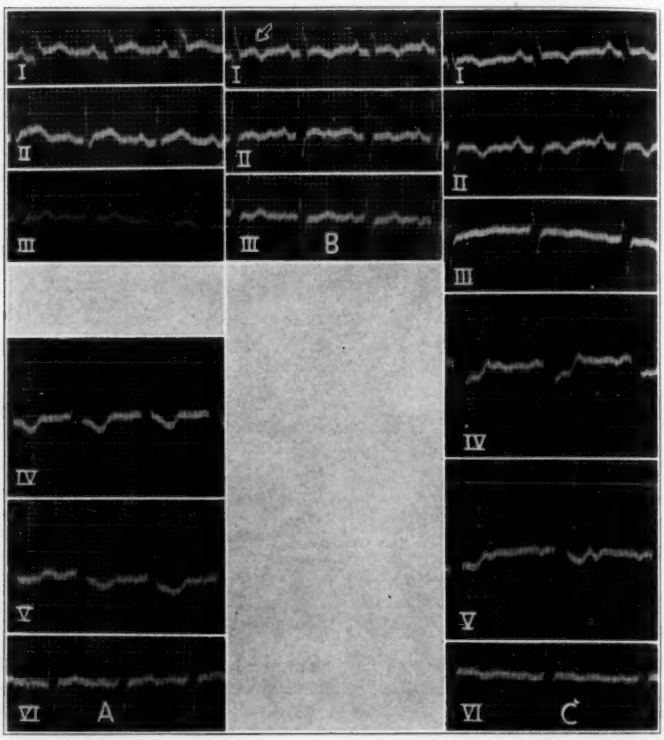


Fig. 2.—Tuberculous pericarditis. *A*, June 24, 1936. Note the elevation of the RST segment in lead I; leads IV and V show a slight depression; lead VI is normal. *B*, July 6, 1936. Note the inverted T_1 wave and the slightly inverted T_2 wave, with the peculiar type of T wave in lead I (described in text). *C*, July 23, 1936. The T wave is inverted in leads I and II. Note the slight depression of the RST segment in lead IV and none in lead V, with maintenance of the initial downward deflection.

shown in figure 2 *B* were also observed by Schwab and Herrmann in cases of pericarditis. This type of T wave by itself is not characteristic of the changes produced by pericarditis, since we have observed it in

association with other conditions. However, when this wave is preceded by a suggestive elevation in the RST segment and accompanied with changes in the precordial leads which conform with the pattern described, it represents a suggestive sign of pericarditis.

The developments that succeed depression of the RST segment of chest leads usually run parallel to those seen in limb leads. They are of some added importance because of their persistence; alterations may still remain after they have disappeared from the limb leads.

Alterations of the T Wave Alone.—In the nineteen cases the only electrocardiographic changes seen in limb leads in our initial studies consisted of flattening or inversion of the T wave in lead I or in leads

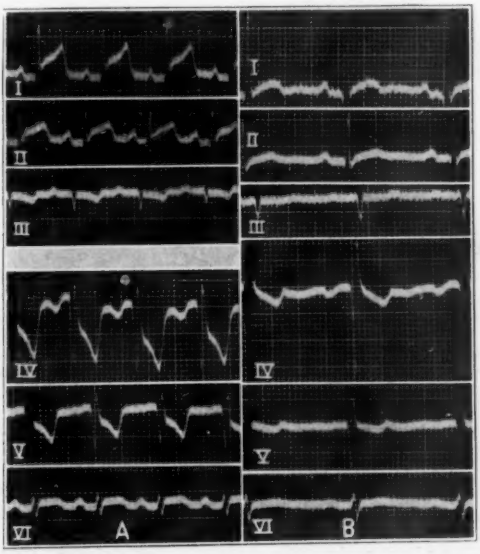


Fig. 3.—A man aged 38 was admitted to the hospital on Aug. 2, 1936, complaining of fever, cough and severe precordial pain. Among other possibilities, coronary occlusion was suspected, and an electrocardiogram was taken. A pericardial friction rub was heard after the electrocardiogram was taken and was suggestive of pericarditis. This patient made a complete recovery and was able to return to his former occupation as a policeman without cardiac symptoms. In view of the typical electrocardiographic pattern—similar to that associated with proved pericarditis, the electrocardiographic changes were considered to be secondary to pericarditis (unknown etiology). *A*, August 3. Note the marked elevation of the RST segment in leads I and II and the depressed RST segment in leads IV and V, with slight elevation in lead VI. *B*, August 17. The patient was considerably improved. The T wave is upright in leads I and II and of somewhat peculiar shape, with no deviation of the RST segment.

I and II, without striking alteration of the RST interval except moderate coving when the T wave was definitely inverted. When healing occurred this type of T wave tended to become flat, and in a few cases we were able to see it finally become normally upright (fig. 6*B*). While an inverted T wave indicates severe derangement of the myocardium, it is not particularly significant of pericarditis unless accompanied with deviation of the RST segment. Cases of this type were of interest to us because an inverted T wave alone without significant deviation of the RST segment was the usual electrocardiographic

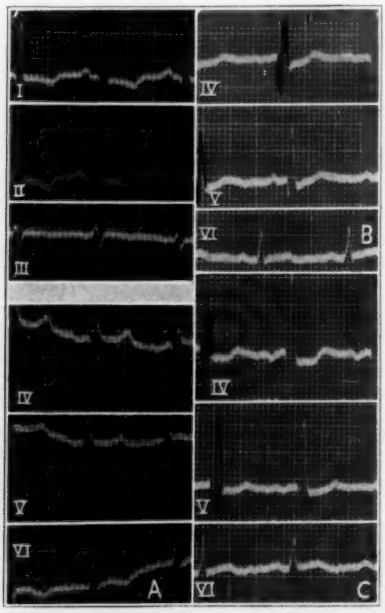


Fig. 4.—Tuberculous pericarditis, June 18, 1936. These electrocardiograms illustrate the presence of a depression in the RST segment in the precordial lead over the area of friction when none was observed in indirect leads. *A*, leads I to VI, with the anterior electrode placed over the apex; *B*, with the anterior electrode placed over the area of friction, over the third interspace to the left of the sternum (note the depression of the RST segment in leads IV and V); *C*, with the anterior electrode placed over the area of friction, over the xyphoid area (note the depression of the RST segment in leads IV and V; see also lead IV in figure 3*C*).

finding in cases of tuberculous pericarditis, whereas deviation of the RST segment was the conspicuous change associated with the more rapidly developing virulent form of pericarditis. This will be discussed further in connection with the causes of these changes.

Comment on Electrocardiographic Changes.—We have suggested that certain electrocardiographic changes in cases of acute pericarditis may have diagnostic significance. We believe this may be the case when the electrocardiogram conforms strictly to a certain pattern chiefly determined by deviations of the RST segment of direct and indirect leads. However, it is to be recognized that the diagnostic importance of the electrocardiogram is definitely limited by several facts: 1. Striking deviations in the RST segment occur mainly in association with the virulent, rapidly developing types; they are infrequently associated with tuberculous pericarditis. 2. Deviation in the RST segment is always transient; it frequently is of brief duration. 3. The deviation in the RST segment may be slight, not present or not characteristic in sufficient leads to be any more than suggestive. 4. In a considerable number of cases the changes, although definite and indicative of cardiac derangement, are not specific of pericarditis (a flat or inverted T wave in lead I in twelve of twenty cases of tuberculous pericarditis). 5. In a certain number of cases no changes are found (twelve in our series of fifty-seven cases).

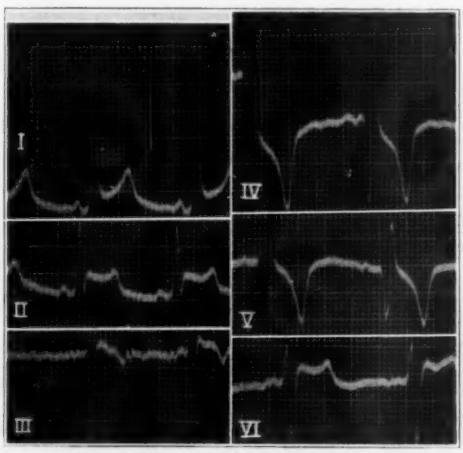


Figure 5.—A clinical diagnosis of uremic pericarditis was made for this patient aged 45. Postmortem examination revealed fibrinous pericarditis, with no fluid in the pericardial sac. Microscopic examination revealed a severe grade of hyaline degeneration and hydropic vacuolation of the epicardial portion of the myocardium (fig. 9). Note the elevation of the RST segment in leads I to III, even though left axis deviation is present. Note the slight depression of the RST segment in lead IV, with none in lead V, and the elevation in lead VI.

These limitations make the diagnosis of acute pericarditis, therefore, still in the main a clinical problem. However, in our opinion the

electrocardiogram, like the roentgenogram, is to be accorded some place in the study of acute pericardial disease, for in our experience it may yield a combination of changes that, so far as we are aware, are not produced by other forms of cardiac disease. How frequently this characteristic electrocardiogram develops is problematic. In our experience it was associated with all forms of acute pericarditis, being noted in twenty-two of forty-seven cases of nontuberculous pericarditis and in two of twenty cases of the tuberculous variety. We have been able to apply these facts advantageously in a few cases; we have

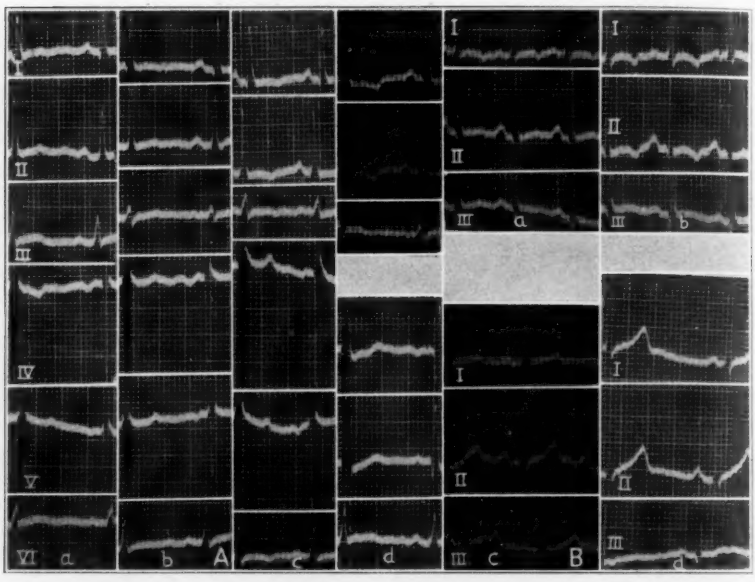


Fig. 6.—*A*, the clinical diagnosis was tuberculous pericarditis; 350 cc. of bloody fluid was obtained on tapping. The patient improved and was discharged in fair condition after a two months' stay in the hospital. *a*, June 18, 1935. The T wave is upright but of low amplitude in leads I and II; aside from a diphasic slightly upright T_6 wave, the precordial leads are within normal limits. *b*, June 21. T_1 is slightly inverted; T_2 is upright, as are also T_4 and T_5. *c*, June 25. T_1 and T_2 are inverted; T_4 and T_5, upright. *d*, July 18. T_1 and T_2 now are deeply inverted; T_4 and T_5 are upright. *B*, tuberculous pericarditis was the clinical diagnosis for a Negro aged 12. The electrocardiograms show a return to normal as the inflammatory process healed. *a*, March 21, 1936. The T wave is inverted in lead I; the T wave is upright but of low amplitude in lead II. *b*, April 2. T_1 and T_2 are now definitely inverted. *c*, June 17. T_1 is upright but of diminished amplitude; T_2, upright. *d*, November 30. T_1 and T_2 are upright. Examination on November 31 revealed cardiac enlargement, with some diminution in the amplitude of the pulsations but no subjective cardiac complaints.

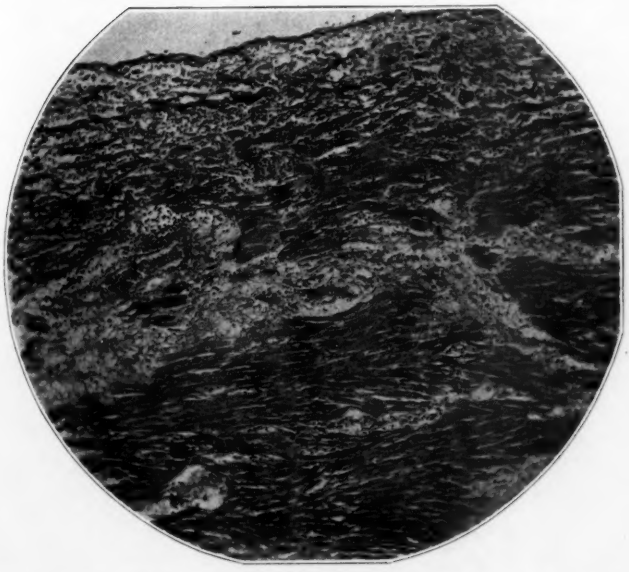


Fig. 7.—An epicardial portion of the myocardium (× 48) of a patient with pneumococcic pericarditis (electrocardiogram, figure 1) showing the myocardial involvement produced by the pericarditis. Note the severe myocardial degeneration and the leukocytic infiltration extending from the pericardium into the muscle structure.

Fig. 8.—Uremic pericarditis (electrocardiogram, figure 5). In this portion of the muscle of the left ventricle note the numerous areas of pale grayish streaks, concentrated chiefly in the subepicardial zone, where they are extensive.

been led by the findings to recognize in five instances acute pericardial disease, subsequently proved, before clinical study led to its being suspected.

CAUSES OF ELECTROCARDIOGRAPHIC CHANGES IN CASES OF PERICARDITIS

The two factors that appear to be the most logical and likely causes of the abnormality of the electrocardiogram in cases of pericarditis are:

Fig. 9.—Magnification (× 230) of a section of the muscle depicted in figure 8, showing an area of hyaline degeneration, dissolution of the sarcoplasm and extensive hydropic vacuolation.

(1) modification of the coronary circulation by increased intrapericardial pressure and (2) direct involvement of the cardiac muscle.

Cardiac Tamponade.—Katz, Feil and Scott,[5] by introducing fluid into the pericardial sac of dogs, produced electrocardiographic changes in the limb leads greatly resembling those which we have been dis-

5. Katz, L. N.; Feil, H., and Scott, R. W.: Electrocardiogram in Pericardial Effusion: Experimental, Am. Heart J. **5**:77, 1929.

cussing. There is therefore little reason to doubt that a large effusion can raise the intrapericardial pressure above the intra-auricular pressure sufficiently to decrease auricular and ventricular filling and thus lower the systemic pressure to the point of impairing the coronary circulation.

We judge that derangement of the blood supply secondary to the tamponading effect on the heart of increased intrapericardial pressure is the mechanism most widely accepted as the cause of the abnormality of the electrocardiogram in cases of pericarditis. So far as deviations of the RST segment are concerned, a study of our material indicates that these changes, which, in degree at least, so strikingly resemble the monophasic curves produced by acute coronary occlusion, can rarely be attributed to such a mechanism. In only three of the twenty-four cases in which the RST deviation was marked and conformed to a certain pattern, which we have described, was the amount of fluid sufficient to suggest this explanation. In two cases the pericardium contained a large quantity of blood, resulting respectively from a stab wound and a ruptured dissecting aneurysm; in the third case a pneumococcic infection produced a large effusion. In eleven of the remaining twenty-one cases the absence of much fluid was confirmed by necropsy, which revealed plastic pericarditis, either with no fluid or with a small amount which was insufficient to exert any effective pressure. In nine of the ten remaining cases in which autopsy was not performed, clinical evidence of any effective effusion was lacking; in the tenth case (pneumococcic pericarditis), we consider that the effusion was not responsible, since the deviation in the RST segment persisted after the pericardium had been opened and drained. Considering the matter from a different point of view, in seven cases of tuberculous pericarditis with massive effusion no deviation was observed in the RST segment, though the T wave was flattened or inverted.

We cannot draw such definite conclusions concerning the relation of cardiac tamponade to a flattened or inverted T wave without deviation in the RST segment. This type of tracing was encountered mainly in our twenty cases of tuberculous pericarditis, and in most of these cases there was accompanying effusion. We are doubtful, however, that the latter produced the change, since in several cases inversion of the T wave was observed to persist for a considerable period after most of the fluid had been removed or had spontaneously disappeared.

Since cardiac tamponade is not a satisfactory explanation of the electrocardiographic changes, we prefer to consider the role of direct muscular injury as a cause of the changes in the RST segment and T wave in cases of acute pericarditis.

Myocardial Injury in Cases of Acute Pericarditis.—Although pathologists have appreciated for a long time that a narrow zone of subendocardial muscle may be severely damaged in cases of acute peri-

cardial disease, this fact has not been widely applied as an explanation of the electrocardiographic findings associated with acute pericarditis. Stengel and Fox [6] stated that the muscle is usually involved; Vaquez,[7] that it often is, and Karsner,[8] that it sometimes is affected in cases of pericarditis. Vaquez [7] placed importance on the muscular changes in cases of pericarditis and attributed "the heart failure sometimes seen in pericarditis to this muscle change." Fowler, Rathe and Smith,[9] in studying experimental pericarditis in dogs, obtained evidence histologically of inflammation, fragmentation and vacuolation involving the superficial muscle tissue. They attributed to this myocardial involvement the inversion of the T wave encountered and were, so far as we are aware, the first to relate the altered electrocardiogram associated with pericarditis to direct muscular injury. Barnes [10] accepted the conclusions just referred to and, as we have stated, attributed certain unusual electrocardiographic findings that are typical in cases of human coronary occlusion associated with pericarditis to direct myocardial change secondary to the pericarditis. He presented, however, no histologic evidence of myocardial change.

Since other suggested explanations seemed to us to be inadequate, the observations we have just cited, which indicate that the electrocardiographic changes in cases of acute pericarditis are the result of accompanying injury, have appealed to us as suggestive. We have attempted to secure additional information bearing on this relation by studying nineteen cases histologically and attempting to determine the extent to which electrocardiographic and histologic changes can be correlated. The histologic changes are recorded in table 2.

Speaking generally, there were striking myocardial changes in a narrow subendocardial zone of muscle over a considerable extent of the ventricular surface in the cases of rapidly developing virulent types of pericarditis, which included the pneumococcic, rheumatic and uremic varieties. In the tuberculous form, which is slower and more insidious in development, generally either there was no demonstrable myocardial involvement, or slight involvement was seen in only occasional focal

6. Stengel, A., and Fox, H.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1915.

7. Vaquez, H.: Diseases of the Heart, translated by G. B. Laidlow, Philadelphia, W. B. Saunders Company, 1924.

8. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926.

9. Fowler, W. M.; Rathe, H. W., and Smith, F. M.: Electrocardiographic Changes Following Ligation of the Small Branches of the Coronary Arteries, Am. Heart J. **8**:370, 1933.

10. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis, Am. Heart J. **8**:734, 1934.

zones, most of the subendocardial muscle being unaffected. The one case which was an exception to this general statement, in that most of the myocardium was destroyed by tuberculous infiltration, will be referred to subsequently.

TABLE 2.—*Histologic Observations in Nineteen Cases of Pericarditis*

Case No	Type of Pericarditis	Changes in T Wave	Days Before Death	Essential Histologic Data for Myocardium
1	Pneumococcic	RST deviation	1	Severe degenerative changes in muscle; cloudy swelling; fragmentation, most marked in subepicardial zone; cellular infiltration into subepicardial portion of myocardium
2	Pneumococcic	RST deviation	1	Same as in case 1; degenerative changes and cellular infiltration marked in subepicardial zone
3	Pneumococcic	RST deviations	2	Same as in case 7
4	Pneumococcic	RST deviation; later, flat T_1; inverted T_2	1	Diffuse severe myocardial degeneration; no predilection to subepicardial zone; no cellular infiltration
5	Pneumococcic	RST deviation later, inverted T_1	2	Vacuolar and fatty degeneration; cloudy swelling, especially marked in subepicardial zone
6	Staphylococcic	RST deviation	3	Degenerative changes in myocardium; cellular infiltration in subepicardial zone
7	Uremic	RST deviation	1	Hyaline degeneration; dissolution of sarcoplasm and hydropic vacuolation, particularly marked in subepicardial zone (fig. 9)
8	Uremic	RST deviation	1	Same as in case 7, but not so marked
9	Uremic	RST deviation	1	Change in muscle as in case 7; slight in degree and especially confined to subepicardial zone
10	Uremic	Inverted T_1	1	Cloudy swelling (slight)
11	Neoplastic	Inverted T_1	1	Extensive carcinomatous infiltration into myocardium; degenerative changes in cardiac muscle
12	Rheumatic	RST originally deviated; inverted T_1	1	Diffuse degeneration; no predilection to subepicardial zone
13	Unknown	RST deviated in precordial leads only	3	Diffuse degenerative changes throughout muscle; dissolution of sarcoplasm; cloudy swelling; vacuolation, most marked in subepicardial zone
14	Tuberculous	Inverted T_1	28	Extensive infiltration of caseous process 1½ to 2 inches (3.8 to 5 cm.) in thickness into myocardium, resulting in destruction of one half to two thirds of ventricular myocardium; cellular infiltration in outer portion of muscle
15	Tuberculous	Inverted T_1	4	Slight infiltration into myocardium (small area)
16	Tuberculous	Inverted T_1	3	Slight cloudy swelling
17	Tuberculous	Flat T_1; inverted T_2	7	No definite change
18	Tuberculous	Inverted T_1	2	No definite change
19	Tuberculous	Inverted T_1	3	No definite change

In attempting to discover the relation between these myocardial changes and the accompanying abnormal electrocardiograms, we wish again to consider separately deviation of the RST segment and inversion of the T wave alone.

Only when there was demonstrable myocardial damage was deviation of the RST segment noted. In all five cases of uremic and pneumococcic pericarditis in which this change was present at death there was extensive involvement of the subepicardial zone of muscle. In three additional cases of pneumococcic and one of rheumatic pericarditis, all associated with extensive myocardial change, deviation of the RST segment was originally shown, though there was only an inverted T wave at the time of death some months later. On the other hand, in five of our cases of tuberculous pericarditis and one case of uremic pericarditis in which necropsy was performed and in which no deviation of the RST segment was noted, there was little or no recognizable histologic evidence of myocardial involvement. In still another case of uremic pericarditis in which there was no deviation in the RST segment we considered the myocardium to be practically normal histologically, the only change noted being slight swelling of an occasional muscle fiber.

This is the only direct evidence that we can present which bears on the question under discussion. We regard it as furnishing a fair correlation between the electrocardiographic changes and the myocardial changes and interpret it as supporting the view that the striking deviation of the RST segment associated with certain forms of acute pericarditis are the result of myocardial change that is gross enough to be demonstrable histologically. However, some indirect evidence to support this view is furnished by the similarity in the electrocardiographic behavior noted in cases of acute coronary occlusion and acute pericarditis.

Two facts concerning deviation of the RST segment in cases of acute coronary occlusion are well established: 1. Deviation of the RST segment occurs only after gross myocardial destruction; it is produced, however, by injured or dying as opposed to dead muscle. With death of the muscle this deviation disappears and gives way to an inverted T wave; for this reason the change is transient and of relatively brief duration. 2. Myocardial death that is slowly produced by gradual as opposed to sudden closure of a coronary artery does not produce striking monophasic curves, though it may cause inversion of the T wave.

The behavior which we have observed in cases of pericarditis is certainly similar. We have seen deviation of the RST segment only when myocardial damage has been demonstrable post mortem (table 2). This change, as we have shown, is transient and is present only during the early stages of myocardial injury; this suggests, as is observed in cases of acute coronary occlusion, that it is the result of injured and dying rather than dead tissue. This is also suggested by the fact that deviation of the RST segment, in our experience, develops chiefly in association with the forms of pericarditis that develop rapidly and malignantly: it is largely absent in cases of the insidious and slowly progressive tuberculous variety of pericarditis. Furthermore, the absence of deviation of

the RST segment in a single case of tuberculous pericarditis in which there was gross destruction of a large portion of the ventricular muscle suggests that when the myocardial injury takes place gradually and insidiously, only inversion of the T wave without deviation results, just as it does with gradual closure of a coronary artery.

Our cases in which a histologic study was made form too small a series on which to base any final conclusions. The evidence furnished, however, as far as it goes, seems to lend definite support to the view that the deviation of the RST segment which is the distinctive electrocardiographic change associated with acute pericarditis, like the similar change associated with acute coronary occlusion, is a result of acute myocardial injury produced by the inflammatory process of acute pericarditis.

So far we have chiefly discussed deviation of the RST segment and have said little concerning the cause of flattening or inversion of the T wave. Since definite alteration of the T wave is an indication of definite myocardial derangement, this abnormal finding must have some definite cause.

With few exceptions, in the cases of acute pericarditis in which there was an initial deviation of the RST segment the T wave became inverted as healing of the pericardial process occurred. The T wave in many instances changed to an upright configuration. Correlation of the electrocardiographic changes with the clinical progress of the pericarditis and the necropsy data suggest that the occurrence of deviation of the RST segment was associated with severe changes in the subepicardial portion of the myocardium, either inflammatory or degenerative. Inversion of the T wave was probably associated with the subacute or subchronic stage and occurred when the pericardial process was healing and the general toxemia was less marked. With tuberculous pericarditis, which, as already stated, occurred in a much less virulent form than the nontuberculous variety, inversion of the T wave, rather than deviation of the RST segment, was the characteristic electrocardiographic change.

In one of the six cases [11] of tuberculous pericarditis in which necropsy was performed gross myocardial damage was present; in the remainder the myocardial damage was slight; in some of these cases we could demonstrate an occasional area in which the inflammatory process had apparently penetrated only superficially into small areas of the myocardium. Aside from these changes little histologic evidence of myocardial damage was seen. The added factor of pericardial effusion in producing changes in the T wave in three of the six cases is to be considered; however, we have observed these changes in the absence of

11. In one case, after pericardiotomy, there were inflammatory changes in the subepicardial portion of the myocardium, which were probably due to secondary infection; this case is omitted from consideration here.

effusion. It should be stated here that it is not unusual to fail to observe demonstrable histologic and other changes to account for the presence of an abnormal T wave. Our findings lead us to attribute the alteration in the T wave in cases of tuberculous pericarditis to the effect of inflammatory changes of the pericardium which produce functional derangement of the underlying muscle and general toxemia and in some instances cause the formation of pericardial fluid.

DIAGNOSTIC IMPORTANCE OF ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PERICARDITIS AND CORONARY OCCLUSION

Not only are the electrocardiographic findings associated with pericarditis and coronary occlusion similar, but the clinical pictures also may be similar. However, as we have indicated, we believe that in cases of pericarditis unassociated with coronary occlusion there are certain distinct features that enable one to differentiate between these two conditions. When the electrocardiographic findings are typical (demonstrated in two cases of our series and consisting of elevation of the RST segment in the three limb leads, its depression in leads IV and V and its elevation in lead VI, with preservation of the initial downward deflection) the differential diagnosis is as a rule comparatively easy, for pericarditis is strongly suggested. We are not acquainted at present with any condition other than pericarditis that can yield a similar combination of electrocardiographic findings, and we have noted no instance of coronary occlusion that has exactly produced them. In all our cases in which necropsy was performed and in which these findings were noted (21 cases) pericarditis alone was present.

The common types of coronary occlusion, namely, the T_1 and T_3 types, produce changes in the limb and precordial leads which are easily differentiated from those typical of cases of pericarditis. The only cases of coronary occlusion in which the electrocardiographic changes may be confused with those seen in cases of pericarditis are the rather rare ones in which the infarction involves both the anterior and the posterior surface of the left ventricle.[12] While this type of infarction produces elevation of the RST segment in the three limb leads, the picture differs definitely from that produced by pericarditis in that, first, the elevation of the RST segment in lead III is slight, while in lead II it is approximately the algebraic sum of the elevations in leads I and III and lead V shows less deviation of this segment than does lead IV; secondly, a Q wave is usually present in leads II and III (neither in the cases in our series nor in the cases reported with which we are acquainted was there

12. Wolferth, C. C.; Wood, F. C., and Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch. Int. Med. **56**:77 (July) 1935.

a Q wave in the electrocardiogram which could be definitely attributed to pericarditis), and, thirdly, the major points of differences are seen in the chest leads. Most important is the fact that in all cases within our experience in which there was both anterior and posterior infarction there was no initial downward deflection in leads IV and V, which is characteristic of infarction of the anterior portion of the left ventricle. In cases of pericarditis the original configuration of the QRS complex is not changed, in spite of striking alteration of the RST interval in both limb and chest leads.

In cases of pericarditis in which elevation of the RST segment is present in leads I and II only, and not in lead III, the electrocardiogram goes far toward establishing pericarditis rather than coronary occlusion as the cause—when the findings of the precordial lead are typical. If extensive pericarditis is present with coronary occlusion the differential diagnosis may of course be extremely difficult—if not impossible. The presence of previous myocardial infarction, an abnormal position of the heart or the effect of digitalis add to the difficulty of the diagnosis. In this connection the importance of serial electrocardiograms is emphasized, since the diagnostic implications, which may have no differential value if based on only one electrocardiogram, may become definite when successive electrocardiograms are available for examination.

SUMMARY AND CONCLUSIONS

The electrocardiographic findings in fifty-seven cases of acute pericarditis of different etiologic types are presented and discussed.

On the basis of these observations it is concluded that in a large majority of cases (80 per cent in this series) electrocardiographic changes are associated with pericarditis. In twenty-one cases (more than 37 per cent) the alteration in the RST segment conformed to a pattern which we regard as fairly characteristic, namely, elevation of the RST segment in the three limb leads, depression of the interval in leads IV and V and elevation of the interval in lead VI, with preservation of the initial downward deflection. In the remainder the inversion of the T wave and minor changes in the RST segment, which are considered important, were noted. In the main, the deviation in the RST segment was observed in association with the more virulent forms of pericarditis, e. g., pneumococcic, uremic and rheumatic; the alteration in the T wave was the outstanding change present in cases of tuberculous pericarditis.

The deviation in the RST segment and the change in the T wave are transient; for this reason it is important to obtain electrocardiographic records at frequent intervals.

The use of precordial leads as an important aid in the diagnosis is herein recorded; additional information was sometimes obtained by placing the anterior electrode over the area of friction.

The basing of a differential diagnosis on the electrocardiographic findings in cases of pericarditis and coronary occlusion is discussed.

Histologic studies of the cardiac muscle were made in nineteen of the cases of our series. From these observations, together with other factors mentioned, it is concluded that invasion of the subpericardial portion of the myocardium by pericarditis is chiefly responsible for the deviation observed in the RST segment.

Frequently, in spite of the presence of frank pericarditis, no electrocardiographic changes are observed. This is probably due to the absence of myocardial involvement or to the presence of an extremely slight grade of involvement.

The chiefs of the various medical, surgical and tuberculous services gave us permission to study and report these cases.

IRON RETENTION IN PERNICIOUS ANEMIA, LEAD POISONING AND MYXEDEMA

W. M. FOWLER, M.D.
AND
ADELAIDE P. BARER, PH.D.
IOWA CITY

Many data have been accumulated on the iron requirements of normal and of pathologic subjects,[1] as well as on the amount of iron which is retained and utilized by patients with anemia of various types.[2] We have shown that patients with hypochromic anemia retain a large amount of iron but utilize only a relatively small percentage of that retained [2a] and that the absence of hydrochloric acid in the gastric juice interferes with the retention of dietary iron but has no effect when large doses of medicinal iron are administered.[3] We have also shown that the degree of anemia which is present has no appreciable effect on the amount of iron retained.[3] The effect of copper and of a liver fraction given in combination with the iron has also been studied,[4] as well as the results obtained with variable amounts of iron.[5] We wish to present in this communication the results of iron balance studies of patients with pernicious anemia, chronic lead poisoning and myxedema.

Supported in part by a grant from Eli Lilly & Co.

From the Department of Internal Medicine, the State University of Iowa.

1. The Iron Requirement of Man, editorial, J. A. M. A. **105**:1917 (Dec. 7) 1935. Farrar, G. E., and Goldhamer, S. M.: The Iron Requirement of the Normal Human Adult, J. Nutrition **10**:241, 1935. Ohlson, M. A., and Daum, K.: A Study of the Iron Metabolism of Normal Women, ibid. **9**:75, 1935. Barer, A. P., and Fowler, W. M.: The Iron Requirements of Adults, to be published.

2. (*a*) Fowler, W. M., and Barer, A. P.: Retention and Utilization of Orally Administered Iron, Arch. Int. Med. **59**:561 (April) 1937. (*b*) Brock, J. F., and Hunter, D.: The Fate of Large Doses of Iron Administered by Mouth, Quart. J. Med. **6**:5, 1937. (*c*) Lintzel, W.: Neuere Ergebnisse der Erforschung des Eisenstoffwechsels, Ergebn. d. Physiol. **31**:844, 1931. (*d*) Reimann, F.; Fritsch, F., and Schick, K.: Eisenbilanzversuche bei Gesunden und bei Anämischen, Ztschr. f. klin. Med. **131**:1, 1936.

3. Barer, A. P., and Fowler, W. M.: Influence of Gastric Acidity and Degree of Anemia on Iron Retention, Arch. Int. Med. **59**:785 (May) 1937.

4. Barer, A. P., and Fowler, W. M.: The Influence of Copper and a Liver Fraction on Iron Retention, Arch. Int. Med. **60**:474 (Sept.) 1937.

5. Fowler, W. M.; Barer, A. P., and Spielhagen, G. F.: Retention and Utilization of Small Amounts of Orally Administered Iron, Arch. Int. Med. **59**: 1024 (June) 1937.

The important clinical features in each of these cases are given in table 1 and the hematologic findings, gastric acidity and basal metabolic rates in table 2.

METHOD

The patients received iron in the form of iron and ammonium citrates in combination with a liver fraction.[6] The amount of iron which they received was determined by analysis of representative samples of this preparation, and the dietary

TABLE 1.—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	57	F	Pernicious anemia	Had received liver extract but in inadequate amounts; rather slow response to liver extract
2	38	F	Pernicious anemia	Had received liver extract in inadequate amounts; slow response to liver extract
3	32	M	Lead poisoning	Had worked in battery repair shop breaking up old storage batteries and making new ones
4	54	F	Lead poisoning	Had used one brand of face powder continuously for 38 years; analysis revealed that this consisted almost exclusively of lead carbonate
5	59	M	Myxedema	Had received thyroid extract intermittently for several years; died of coronary occlusion
6	52	F	Myxedema	Gradually increasing symptoms for 10 years prior to admission to hospital; presented all characteristic features
7	69	F	Myxedema	Increasing symptoms for 3 years; presented all characteristic features

TABLE 2.—*Laboratory Data* *

Patient	Hemoglobin, %	Hematocrit Reading, %	Erythrocytes, %	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	62	90	92	0.67	0.97	0.69	0	—
2	82	89	93	0.88	1.08	0.92	0	+24
3	56	74	67	0.83	1.10	0.75	—	—
4	56	68	63	0.88	1.07	0.82	0	—
5	85	95	87	0.97	1.09	0.89	0	—38
6	49	65	58	0.84	1.12	0.75	Normal	—41
7	55	71	65	0.84	1.09	0.77	Normal	—35

* The hemoglobin, hematocrit and erythrocyte values are given in percentage of normal values, as calculated from the tables of Osgood (A Textbook of Laboratory Diagnosis, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1935, p. 420).

intake of iron was calculated from the tables of Rose.[7] The procedures were the same as those described in a previous report.[2a] The balance studies were preceded by a three day period of adjustment, during which the patients received the regular balance diets. This was followed by a six day control period, during which they received no medicinal iron. Patients 1, 3 and 5 were studied for only one period and did not receive additional iron, and patient 7 was studied for two six day periods before the administration of iron was begun. The control period for patient

6. The preparation used was lextron.

7. Rose, Mary S.: Laboratory Handbook for Dietetics, ed. 3, New York, The Macmillan Company, 1929.

TABLE 3.—*Results of Balance Studies*

Patient	Period	Average Daily Nitrogen Balance, Gm.			Average Daily Phosphorus Balance, Gm.			Average Daily Iron Balance, Mg.			Erythrocytes, Millions	Hemoglobin, Gm.	Hematocrit Reading, %
		Intake	Excretion	Balance	Intake	Excretion	Balance	Intake	Excretion	Balance			
1	1	13.484	11.917	+1.567	1.668	1.603	+0.065	19.98	23.04	− 3.06	4.665	8.905	38.5
2	1	13.484	15.620	−2.136	1.668	1.787	−0.119	19.98	33.82	− 13.84	4.470	11.715	40.0
	2	14.492	16.579	−2.087	1.701	2.231	−0.530	283.98	187.21	+ 96.77	4.510	12.340	40.0
	3	14.492	15.620	−1.128	1.701	1.901	−0.200	283.98	210.55	+ 73.43	4.460	12.200	41.5
3	1	10.114	8.613	+1.501	1.499	0.959	+0.540	12.75	7.38	+ 5.37	3.343	8.210	30.0
4	1	9.843	7.334	+2.509	1.442	1.090	+0.352	11.49	9.22	+ 2.27	3.150	8.034	29.0
	2	11.346	8.863	+2.483	1.505	1.219	+0.286	263.78	110.54	+153.24	3.030	8.420	28.0
	3	10.449	8.842	+1.607	1.440	1.247	+0.193	269.35	115.96	+153.39	3.330	8.830	30.0
	4*	11.121	9.330	+1.791	1.508	1.263	+0.245	269.83	322.04	− 52.21	3.683	10.320	32.5
	5	11.126	10.424	+0.702	1.510	1.311	+0.199	269.81	250.25	+ 19.90	3.530	10.090	32.0
5	1	10.667	7.739	+2.928	1.478	0.933	+0.545	12.19	4.53	+ 7.66	4.360	12.488	39.0
6	1	9.795	14.121	−4.326	1.444	1.545	−0.101	11.91	5.81	+ 6.10	2.910	7.058	28.0
	2	10.789	13.940	−3.151	1.472	1.067	+0.405	275.69	160.54	+115.15	3.200	7.077	29.0
	3	11.513	12.276	−0.763	1.520	1.100	+0.420	276.38	190.65	+ 85.07	3.470	7.058	28.5
	4	11.716	12.161	−0.455	1.534	1.142	+0.392	276.53	187.29	+ 89.23	3.470	7.415	29.0
7	1	9.811	7.968	+1.843	1.454	1.177	+0.277	11.78	10.72	+ 1.06	3.283	7.945	30.5
	2	9.404	11.034	−1.630	1.417	1.426	−0.009	11.62	11.64	− 0.02	3.110	8.378	28.5
	3	10.054	12.305	−2.251	1.377	1.627	−0.250	262.96	160.46	+102.50	2.880	8.173	29.0
	4	10.008	16.750	−6.672	1.373	1.623	−0.250	262.77	180.49	+ 82.28	3.180	8.267	31.0
	5	10.549	12.558	−2.009	1.429	1.378	+0.051	263.43	227.26	+ 36.18	3.160	8.868	30.0

* Forty-five days between periods 3 and 4. Twelve capsules per day of a combination of iron and liver extract were taken during that time.

2 was complicated by menstruation, so that the markedly negative iron balance is partially explained on this basis. All balance periods were of six days' duration, and carmine was used to mark the stools at the beginning and at the end of each period. The excreta were carefully collected and stored in glass or porcelain-lined containers. Nitrogen was determined by the Kjeldahl method, phosphorus by the method of Fiske and Subbarow [8] and iron by the method of Reis and Chakmakjian.[9]

The complete results of the balance studies are given in table 3, and a summary of the data on iron retention is given in table 4.

RESULTS

Pernicious Anemia.—Various iron balance studies have been made on patients with pernicious anemia. Queckenstedt [10] has stated that there is no correlation between the fall in the blood count and the rate of urinary excretion of iron. Riecker [11] has shown that the iron content of the serum is higher during a relapse in pernicious anemia but returns

TABLE 4.—*Average Daily Iron Balance by Periods*

Patient	Iron Balance, Mg.					Total Iron Retained,* Mg.	Percentage of Iron Retained
	Control Period	Period 1	Period 2	Period 3	Period 4		
1	— 3.06	.....	.....	.....	.....	—	..
2	—13.84	+ 96.77	+ 73.43	.....	.....	1,021.20	29
3	+ 5.37	.....	.....	.....	.....	—	..
4	+ 2.27	+153.24	+153.39	—52.21	+19.90	1,645.92	25
5	+ 7.66	.....	.....	.....	.....	—	..
6	+ 6.10	+115.15	+ 85.07	+89.23	.....	1,736.70	34
7	+ 1.06	— 0.02†	+102.50	+82.28	+36.18	1,325.76	27

* Exclusive of control periods.
† No medicinal iron was given.

to normal during a remission and that a remission is accompanied with an increase in the excretion of iron. Gibson and Howard [12] have demonstrated that a favorable iron balance may be readily established in patients with pernicious anemia when a diet rich in iron is given and that iron retention may occur in the presence of a negative nitrogen balance.

Patient 1 of our series was in a negative iron balance of 3.06 mg. per day while receiving a diet containing 19.98 mg. of iron. She was in positive nitrogen balance. Patient 2 was in a markedly negative

8. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

9. Reis, F., and Chakmakjian, H. H.: Colorimetric Method for Quantitative Determination of Iron in Blood in the Form of Dispersed Prussian Blue, J. Biol. Chem. **92**:59, 1931.

10. Queckenstedt, H.: Untersuchungen über den Eisenstoffwechsel bei der perniziösen Anämie, mit Bemerkungen über den Eisenstoffwechsel überhaupt, Ztschr. f. klin. Med. **79**:49, 1914.

11. Riecker, H. H.: Iron Metabolism in Pernicious and Secondary Anemia, Arch. Int. Med. **46**:458 (Sept.) 1930.

12. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, Arch. Int. Med. **32**:1 (July) 1923.

iron balance during the control period, although this was partially accounted for by the menstrual loss of blood. Both of these patients were in a partial remission induced by liver extract, but improvement had ceased in spite of the continued administration of a potent liver extract. The hemoglobin value for both increased to normal with the subsequent administration of iron and liver extract. With the administration of iron and ammonium citrates in combination with a liver fraction, it was found that patient 2 retained a large amount of iron (tables 3 and 4). During the first period of administration of iron she received 283.98 mg. per day and retained 96.77 mg. During the second period, with a similar intake, she retained 73.43 mg. per day. For the entire period of administration of iron she retained 29 per cent of the amount given. When the same preparation of iron with a liver fraction was administered in similar amounts to a group of patients with hypochromic anemia, the retention varied from 13.2 to 31.1 per cent, with an average of 20.4 per cent.[4] Although the hemoglobin value for patient 2 increased only 0.485 Gm. per hundred cubic centimeters of blood in the twelve days of the balance study, there was a further increase after the balance study was completed, whereas the hemoglobin value had previously been nearly stationary with liver extract alone.

Lead Poisoning.—Two patients (3 and 4) with chronic lead poisoning were studied in a similar manner. Patient 3 was under observation for only one six day period with no medicinal iron. During this period he retained 5.37 mg. of iron per day from the diet alone. Patient 4 retained 2.27 mg. from the dietary iron and was studied for four additional balance periods while receiving medicinal iron. She was given a combination of iron and ammonium citrates with a liver fraction and received from 263.78 to 269.83 mg. of iron per day. During the first two periods of administration of iron 153.24 and 153.39 mg., respectively, was retained, during the third period there was a negative balance of 52.21 mg. per day and in the fourth period only 19.9 mg. was retained per day. For all four periods 25 per cent of the iron which was administered was retained, an amount which is but slightly higher than the average of 20.4 per cent for the patients with hypochromic anemia previously reported. During the first twelve days the hemoglobin value increased 0.066 Gm. per day, but during the last twelve days no increase occurred. There was an interval of forty-five days between these periods, during which the patient received the liver and iron continuously.

Hypothyroidism.—Three patients with typical myxedema were similarly studied. Patient 5 was in a positive iron balance of 7.66 mg. per day with a dietary intake of 12.19 mg., in spite of the fact that he had achlorhydria. Patient 6, with normal gastric acidity, was in a posi-

tive balance of 6.1 mg. from a diet containing 11.91 mg. of iron. With the administration of iron and ammonium citrates and a liver fraction, large amounts of iron were retained, and during the three periods she retained 34 per cent of the iron which was administered. During this time there was but a slight increase in the hemoglobin value—0.357 Gm. in eighteen days. Thyroid extract was being administered during this time. For patient 7 there were two control periods in which the iron balances were +1.06 and —0.02 mg. per day, respectively. During the following three periods she retained 27 per cent of the iron administered. The increase in the hemoglobin value during this period was small, amounting to 0.027 Gm. per day. This patient was also receiving thyroid.

COMMENT

The results of the iron balance studies of these patients show a retention of iron varying from 25 to 34 per cent. This is slightly, but not significantly, greater than the retention which was obtained with similar amounts of the same preparation when given to a group of patients with hypochromic or iron deficiency anemia.[4] This indicates that the type of anemia does not influence the amount of iron which is retained and is in keeping with the previous report [3] showing that the degree of anemia does not influence the retention of iron. The results reported here were obtained for patients with three entirely different types of anemia.

Patients with pernicious anemia retained 29 per cent of the iron, and the hemoglobin value increased at the rate of 0.04 Gm. per day. It has been shown that iron is advantageous in certain of these cases, particularly when the hemoglobin value and the erythrocyte count have increased to a certain level and have then remained stationary in spite of continued liver therapy. Such was the case in these two patients with pernicious anemia, and after the balance studies were discontinued the hemoglobin values continued to increase with the administration of the combination of iron and liver extract.

One patient with chronic lead poisoning retained 25 per cent of the iron administered. The hemoglobin response to this amount of iron was not extremely rapid (0.06 Gm. per day) but was such that the medication seemed to be advantageous. There was no evidence of a deficiency of iron in these patients, but nevertheless the retention of iron and the hemoglobin response obtained with the combined liver extract and iron justify its use.

There is some dispute as to the proper therapy for the anemia associated with myxedema. Baldridge and Greene [13] have shown that

13. Baldridge, C. W., and Greene, J. A.: Absence of Response of Anemia of Myxedema to Liver Extract, Proc. Soc. Exper. Biol. & Med. **31**:1035, 1934.

there is no response to the administration of liver extract in these patients. Lerman and Means [14] have stated the opinion that liver is of value in accelerating or initiating the erythrocyte response in certain cases. They showed that thyroid extract alone may cause a slow improvement in the anemia but that the anemia persists in some cases. They concluded that iron produced the most rapid improvement. Our results from the administration of a combined liver and iron preparation show that 27 and 34 per cent of the iron, respectively, was retained by two patients and that the hemoglobin response amounted to 0.019 and 0.027 Gm., respectively, per day. Although this is not a particularly rapid response, it is more rapid than that obtained with thyroid extract or liver extract alone. Whether or not this combination of liver and iron is more advantageous than iron alone cannot be answered from this experiment. However, it has been shown that iron is retained under these circumstances in this type of anemia and that a satisfactory hemoglobin response ensues.

SUMMARY

Iron baiance studies were made of patients with pernicious anemia, chronic lead poisoning and myxedema. Iron and ammonium citrates was administered in combination with a liver fraction, and it produced a retention of from 25 to 34 per cent of the administered iron. This is comparable to the amount of iron retained in hypochromic anemia under similar circumstances.

14. Lerman, J., and Means, J. H.: Treatment of the Anemia of Myxedema, Endocrinology **16**:533, 1932.

GRANULOCYTOPOIETIC FRACTION OF YELLOW BONE MARROW

C. M. MARBERG, PH.D.
AND
HAROLD O. WILES, PH.D.*
CHICAGO

At the meeting of the American Medical Association in Milwaukee in 1933 Dr. C. H. Watkins, of the Mayo Clinic, announced that a strained preparation of yellow bone marrow had been beneficial in cases of granulocytopenia. After the use of the yellow marrow, monocytosis occurred and was rapidly followed by an increase in the number of polymorphonuclear neutrophils. This reaction occurred generally within twenty-four to forty-eight hours after ingestion of the marrow.[1] A report of this work has not yet been published by Dr. Watkins.

Shortly after this announcement Dr. M. J. Flipse, of Miami, Fla., successfully used yellow bone marrow for a series of patients suffering from granulocytopenia.[2] This preparation is extremely unpalatable and has the further disadvantage that it must be taken in very large doses (60 to 120 Gm. or more daily), in some cases large enough to interfere with normal metabolism. Dr. Flipse expressed to Dr. F. Fenger, of Armour & Co., the need of a potent concentrate of the active principle of yellow bone marrow, and Dr. Fenger, in turn, presented the problem to one of us (C. M. M.), who was at the time the Armour Fellow in the Otho S. A. Sprague Memorial Institute.

---

* Armour Fellow in the Otho S. A. Sprague Memorial Institute.

From the Otho S. A. Sprague Memorial Institute and the Department of Pathology, the University of Chicago.

This paper contains the essential features of a preliminary report presented to the Medicinal Section of the American Chemical Society at the meeting in Cleveland on Sept. 11, 1934. Publication was withheld pending the accumulation of a larger series of clinical data or the development of a reliable method of animal assay which would establish beyond any doubt the activity of our material and lead the way to further chemical purification of the granulocytopoietic substance. We are now publishing our data because of the recent appearance of a paper under an almost identical title by J. Zichis (Granulocytopoietic Fractions of Yellow Bone Marrow, J. Lab. & Clin. Med. **22**:231 [Dec.] 1936), which will be criticized in the body of this paper. A preliminary report was recently published by us (Yellow Bone Marrow Extracts in Granulocytopenia: Preliminary Report, J. A. M. A. **109**:1965 [Dec. 11] 1937).

1. Watkins, C. H.: Personal communication to the authors.

2. Flipse, M. J.: Preliminary report to the meeting of the Florida State Medical Society, 1934.

CHEMICAL PREPARATION

In the preparation of such an active concentrate the first consideration was the undesirability of the large amount of free fat present in yellow bone marrow. There was no reason to believe that either fat or fatty acids were necessary for granulocytopoiesis, and it seemed improbable that any of the less abundant saponifiable constituents (phosphatides, for instance) would be necessary. Accordingly, the first step taken was the removal of the saponifiable fraction.

The beef marrow was subjected to saponification with an excess of alcoholic potassium hydroxide at the refluxing temperature. After dilution of the soap solution with water, the nonsaponifiable fraction was extracted in the usual way (ether, ligroine or, better, ethylene dichloride was used). The solvent was removed in vacuo, and a reddish brown semicrystalline waxy residue remained. The yield varied between 0.1 and 0.2 per cent of the weight of the crude marrow used. This residue was dissolved in a bland oil (peanut, corn or cottonseed) for oral administration in such concentration that each drop (0.05 cc.) was equivalent to 2 Gm. of strained yellow bone marrow. It has been shown by clinical test that practically all the activity of the original marrow is contained in the nonsaponifiable fraction.

The yellow bone marrow used in this work was from the tibias and femurs of cattle, being obtained in clean condition, free from bone, blood and other extraneous material. Over 250 Kg. has been worked up in our laboratory in the following manner:

Saponification Number.—A 1 Kg. sample of the crude marrow was repeatedly ground until a uniform sample could be obtained. The saponification number was determined by the usual method:

4.4817 Gm. required 761.16 mg. of potassium hydroxide
5.8172 Gm. required 990.73 mg. of potassium hydroxide
Average value for saponification number, 170.1

Saponification and Extraction.—For lot 2 (Oct. 20, 1933) 4,200 Gm. of fresh beef yellow bone marrow was added slowly to a hot solution of 1,250 Gm. of commercial potassium hydroxide (92 per cent) in 3,000 cc. of alcohol. The material was boiled under a reflux condenser, agitation being accomplished by blowing a stream of nitrogen through the material. When the saponification was complete, in one to two hours, 3,000 cc. of water was added, and the resulting clear, dark brown solution was allowed to cool to room temperature; then it was extracted with ethylene dichloride as follows: Two liters of the soap solution was shaken with 1 liter of ethylene dichloride, of which about 525 cc. went into solution. The rest separated fairly readily and was drawn off. For each of the next four extractions 500 cc. of ethylene dichloride was used. These volumes were recovered almost quantitatively. The combined ethylene dichloride extracts were dried over sodium sulfate after being washed with water. The rest of the soap solution was similarly extracted, and the combined extracts were evaporated in vacuo at a bath temperature not exceeding 50 C. The residue was a deep reddish brown oil, which solidified on cooling. The yield, 4 Gm., represented 0.1 per cent of the weight of bone marrow used.

For lot 4, 15 Kg. was worked up in the same way and yielded 20.5 Gm. of residue, and for lot 5, 14.8 Kg. was worked up and yielded 20.6 Gm. Our yields have varied between 0.1 and 0.2 per cent—we have never even approached the figure given by Zichis,[3] whose material undoubtedly contains free fat, since the amount of alkali used by him in his first preparation (6 liters of 3 per cent alcoholic potassium hydroxide for 2 Kg. of bone marrow) is about half that required for complete saponification of the fats. Our material contains a large amount of cholesterol, in contrast to his, which "gave a negative test for sterols." We have also been able to isolate a small amount of crystalline carotene from our preparation.

EXPERIMENTAL TESTING OF GRANULOCYTOPOIETIC AGENTS

The difficulty of testing our preparations has led us to investigate the possibility of the experimental induction of granulocytopenia in animals. In attempts to determine the etiologic factors of the disease many investigators have also sought to produce the condition in animals. Kracke and Parker [4] were able to produce neutropenia in only an occasional animal of a large series by intravenous injection of hydroquinone, catechol, aniline, para-aminophenol, quinone and phenol, but they were not able to reproduce the clinical picture. Madison and Squier [5] were able to produce granulocytopenia in only one rabbit of a series to which they administered aminopyrine. Stenn,[6] in this laboratory, gave aminopyrine intravenously over a long period to a series of one hundred and twenty animals (guinea pigs, rabbits and monkeys) without success. He also superimposed treatment with aminopyrine on experimental anemia and on infections in animals but failed to get results. Many workers [7] have unsuccessfully attempted to produce the condition by inoculation of animals with organisms isolated from patients dying of the disease. Yet a few, for instance, Fried and Dameshek,[8] have

3. Zichis, J.: Granulocytopoietic Fractions of Yellow Bone Marrow, J. Lab. & Clin. Med. **22**:231 (Dec.) 1936.

4. Kracke, R. R., and Parker, F. P.: The Etiology of Granulopenia (Agranulocytosis), J. Lab. & Clin. Med. **19**:799 (May) 1934.

5. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**:755 (March 10) 1934. Squier, T. L., and Madison, F. W.: Primary Granulocytopenia Due to Hypersensitivity to Amidopyrine, J. Allergy **6**:9 (Nov.) 1934.

6. Stenn, Fred: Etiology of Agranulocytosis, Arch. Path. **20**:902 (Dec.) 1935; The Etiologic Relationship of Amidopyrine to Agranulocytosis, J. Lab. & Clin. Med. **20**:1150 (Aug.) 1935.

7. Lovett, B.: Agranulocytic Angina, J. A. M. A. **83**:498 (Nov. 8) 1924. Linthicum, F. H.: Experimental Work with the Bacillus Pyocyaneous: Report of a Case of Pyocyanic Stomatitis with Agranulocytic Leucopenia, Ann. Otol., Rhin. & Laryng. **36**:1093 (Dec.) 1927. Keeney, M. J.: Pyocyanic Angina, with Agranulocytosis, California & West. Med. **33**:503 (July) 1930.

8. Fried, B. M., and Dameshek, W.: Experimental Agranulocytosis, Arch. Int. Med. **49**:94 (Jan.) 1932.

reported the induction of primary granulocytopenia in rabbits by intravenous injection of Salmonella suipestifer. Their data do not indicate a reproduction of the clinical picture, but rather a temporary neutropenia, such as generally follows the injection of killed organisms. Piersol and Steinfield [9] injected Berkefeld filtrates and supernatant fluids from cultures and called attention to the fact that injections of peptones and a large number of proteins cause temporary leukopenia.

Dennis [10] placed a capsule containing a broth culture of pyogenic bacteria in the abdomen of each of a series of rabbits and obtained nonconclusive results with Staphylococcus aureus, Streptococcus haemolyticus and Bacillus proteus. With a large dose of Streptococcus viridans in relation to the size of the animal, he obtained sustained and marked granulocytopenia. Zichis [3] used the technic of Dennis and Staph. aureus as the organism with a series of forty-six rabbits. Of these, only "seventeen developed granulocytopenia, nine died without showing any change in the leucocytic picture, and twenty recovered without any apparent ill effects." He described no control animals and gave data for only nine of the rabbits used. According to Zichis' own data, four of these rabbits (no. 2, 5, 6 and 9) showed a distinct decrease in the total leukocyte count after a temporary rise while receiving his medication. At most, his results are only indicative, being not at all conclusive. We believe that the Dennis technic as used by Zichis is not at all reliable and that for the present at least it is necessary to use human subjects.

Patients with granulocytopenia are generally so ill that it is hard to deny them anything that may be beneficial, and so they are generally given several medicines simultaneously. It is therefore difficult to determine the efficacy of any one preparation. However, we were able to obtain reports of a few cases in which other medication was discontinued in favor of our concentrate, and the results obtained were convincing. Also, the relatively prompt response to yellow bone marrow concentrate often distinguishes its effect from the possible action of other therapeutic agents.

We tested our material on a series of six normal persons in our laboratory and found no effect on the leukocyte counts. Flipse [11] found that only one of five normal persons in his laboratory responded. This person showed an increase to 12,000 leukocytes within twenty-four hours after taking 10 Gm. of refined whole yellow marrow. The same

9. Piersol, G. M., and Steinfield, E.: Granulopenia (Granulocytopenia), with Special Reference to Classification and Benign Types, Arch. Int. Med. **49**:578 (April) 1932.

10. Dennis, E. W.: Experimental Granulopenia Due to Bacterial Toxins Elaborated in Vivo, J. Exper. Med. **57**:993 (June) 1933.

11. Flipse, M. J.: Personal communication to the authors.

person showed an increase from a normal total leukocyte count, of 7,000, to 21,000 (86 per cent polymorphonuclears) within twenty-four hours after taking a teaspoonful of the concentrate.

CLINICAL OBSERVATIONS

The effect of our preparation on patients with granulocytopenia is illustrated in the following briefs of cases in which it was tested. These summaries and the data on the blood counts were taken from the records of the respective hospitals or attending physicians and are presented in chronological order. The diagnoses given are those of the attending physicians. Four of the patients (cases 1 to 4) were treated with material prepared in this laboratory; subsequent patients received a concentrate prepared by essentially the same method in the pharmaceutic department of Armour & Co.

CASE 1.—Mrs. H. V. (a patient of Dr. E. M. Poser, Columbus, Wis.) was first seen on March 10, 1934. She complained of pain in the cervical, dorsal, lumbar and sacro-iliac regions, with accompanying difficulty in walking. Physical examination revealed no abnormality except pain and lessened mobility of the spine and in the sacro-iliac region.

The patient was given liver extract with iron orally until her return on March 14. A blood count at that time showed: hemoglobin, 80 per cent; red blood cells, 4,800,000, and leukocytes, 2,600, with 27 per cent granulocytes. Treatment with yellow bone marrow concentrate was begun immediately—20 drops was given three times the first day; 10 drops, three times the second day, and 5 drops, three times a day, thereafter. The next count (March 23) showed: hemoglobin, 80 per cent; red blood cells, 5,000,000, and leukocytes, 5,400, with 35 per cent granulocytes. The succeeding count, details of which are not available, was within the normal range. Clinical improvement followed immediately the restoration of a normal blood picture, and the patient was relieved of the arthritic condition. She remained in good health until her death from pneumonia two years later.

The diagnosis was chronic arthritis with leukopenia.

CASE 2.—Miss E. D. (a patient of Dr. M. Simkin) was an office worker aged 34. She noticed pain and numbness about the gums and tongue on April 28, 1934. On the two following days the pain increased, the temperature rose to 101 F. and was accompanied with malaise, nausea and vomiting and she was obliged to leave her work. When seen by her physician on May 1 she complained of severe pain in the mouth, general malaise and aching, lack of appetite and restlessness.

She had anemia in about 1922 and in 1930 and an infection of the upper respiratory tract, accompanied with loss of weight, an afternoon rise of temperature, diminished breathing and dulness over the bases of both lungs, with subcrepitant râles. Neither examinaton of sputum nor roentgenograms definitely established a diagnosis of tuberculosis. Four months' rest resulted in complete recovery and a gain in weight. The tonsils were removed in 1931. Two years later, purpuric spots and ecchymoses developed. A blood count showed: hemoglobin, 70 per cent; erythrocytes, 4,000,000; leukocytes, 9,000, and platelets, 100,000. The symptoms abated with liver therapy, but she continued to have

occasional purpuric spots. In June 1933 she had abdominal pain, with albuminuria, but recovered after a week's rest in bed. Her symptoms had been present for three days and were increasing in severity. She had not taken aminopyrine.

Physical examination revealed no abnormality except swollen and spongy gums and bleeding ulcerations under the upper incisors and over the lingual aspect of the left molars. The temperature was 101.5 F. and the pulse rate 100.

Local treatment was instituted. She felt somewhat better the following day but was weak and languid. The temperature was 100.5 F., and a blood count showed 4,000 leukocytes, which was thought to be a low count, but not alarming. The ulceration under the upper incisors had disappeared. The next day (May 3) the pain in the ulceration about the upper molars on the left side was so severe as to require morphine. The ulcer had enlarged and deepened and was covered with a white membrane.

The blood count on the morning of May 4 showed: hemoglobin, 70 per cent; erythrocytes, 4,230,000, and leukocytes, 2,900, with 60 per cent lymphocytes and 38 per cent neutrophils. She was hospitalized and given liver extract and pentnucleotide parenterally. Ten cubic centimeters of pentnucleotide caused a severe reaction, and it was necessary to give subsequent injections in divided doses. Three cubic centimeters of liver extract was given parenterally every second day and 16 to 20 cc. of pentnucleotide every day.

The patient's condition changed little during the two following days; the leukocyte count reached its lowest level on May 6 (1,500, with 36 per cent neutrophils). There was little change on the seventh day; blisters appeared on the lips on the eighth day and broke the following day, leaving painful indurated ulcers at their sites. Treatment with extralin was thereupon started, 4 capsules being given three times a day. The patient felt definitely better on May 12, although the ulcers had not changed in appearance. The blood count had improved, showing 3,400 leukocytes, with 63 per cent neutrophils. The temperature still ranged from 99 to 100 F. There was slow clinical improvement during the following days. On May 16 there were 5,700 leukocytes, with 76 per cent neutrophils. The use of liver extract was discontinued.

On May 20, with the leukocytes numbering 6,500, the ulcers in the mouth and on the lips showed definite evidence of healing. The patient strenuously objected to the injections of pentnucleotide, and the dose was reduced to 12 cc. on May 21 and to 8 cc. on May 22, when the leukocyte count was 4,150, with 84 per cent neutrophils. The ulcers were then almost completely healed. Treatment with pentnucleotide and extralin was discontinued on May 23.

The leukocyte count had fallen to 4,250 on May 24, and although the patient felt well and had no fever, the blood picture was not considered satisfactory. Two 0.5 Gm. enteric-coated capsules [12] of the nonsaponifiable residue of yellow bone marrow were given, and the dose was repeated the following day. On May 26, as the leukocyte count remained at 4,250, she was given yellow bone marrow concentrate (in oil), 105 drops per day. She was discharged from the hospital the following day, the count showing 4,500 leukocytes. On May 28 (forty-eight hours after the start of treatment with yellow bone marrow concentrate in oil) the leukocyte count was 7,500. The dose was reduced to 75 drops for one day and was then gradually reduced to 40 drops by June 23.

In order to test the potency of the concentrate, the medication was stopped from June 29 to July 5. The leukocyte counts were: June 29, 6,000; July 2, 5,800,

12. It was later learned that the capsules were too heavily coated and would not open in the gastro-intestinal tract.

and July 5, 4,000. Treatment with the concentrate (60 drops) was immediately resumed, and the next count (July 9) showed 7,500 leukocytes. The yellow bone marrow concentrate was gradually withdrawn, and the blood count remained within normal limits.

In March 1937 the patient had a recurrence but was seen before the sublingual ulcer had extended far. With the use of yellow bone marrow concentrate the leukocyte count rose from 3,500 to 7,500 in less than seventy-two hours, and the angina was controlled.

The diagnosis was recurrent agranulocytic angina (table 1 and chart 1).

CASE 3.—Mrs. L. C., aged 56, a patient in the University of Chicago Clinics, entered the hospital on July 3, 1934, with pain in the lower part of the back and sciatica. She had mastectomy for carcinoma of the left breast three years previously. She returned in May 1934, with a local recurrence; she was given local roentgen therapy and was discharged on June 6. The blood count on May 15 showed: hemoglobin, 80 per cent; erythrocytes, 5,200,000, and leukocytes, 7,400. The present symptom dated from about that time.

Physical examination on July 3 revealed nothing significant except four or five small metastases in the operative scar on the left side of the chest. The blood count showed: hemoglobin, 75 per cent; erythrocytes, 4,370,000, and leukocytes, 4,050.

From July 3 to 9 a total of 2,150 roentgens was given over the left side of the chest and the lumbosacral region; codeine, phenobarbital and aminopyrine (the average dose of the last was about 0.7 Gm. per day) were given for sedation. On July 9 the blood count showed 3,100 leukocytes; roentgen treatment was suspended. Sedatives were given as before. On July 13 the leukocyte count was 2,600, with 74 per cent polymorphonuclears. The leukocyte count fell to 1,900 on July 15.

Treatment with 1,250 roentgens was given between July 17 and 20. On July 21 the leukocyte count was 900, and on July 22, 850. She was given a transfusion of 500 cc. of citrated blood. Irradiation and treatment with aminopyrine were discontinued, and on July 23 treatment was started with yellow bone marrow concentrate, 35 drops three times a day. The blood count on that day showed: erythrocytes, 4,440,000, and leukocytes, 950, with 44 per cent polymorphonuclears, 2 per cent eosinophils, 9 per cent basophils, 35 per cent lymphocytes and 10 per cent monocytes.

The total leukocyte count rose to 1,800 on July 26 and to 1,700 on July 27, with little change in the differential picture except a rise in the monocyte count to 20 per cent on July 26. On July 28 there was a sharp rise in the granulocyte count to 57 per cent of 1,900; the patient felt better. The increase continued—July 30, 3,900 leukocytes, with 65 per cent neutrophils; July 31, 4,000 leukocytes, with 71 per cent neutrophils; August 1, 3,600 leukocytes, with 77 per cent neutrophils. She was discharged on August 2 for care at home. The subsequent course is not known, except that she died some time later.

The diagnosis was leukopenia associated with carcinomatosis (table 2 and chart 2).

CASE 4.—Miss D. S., an x-ray technician aged 24, was admitted to St. Luke's Hospital on Oct. 23, 1934. She complained of sore throat of twenty-four hours' duration and of increasing severity, malaise and chills. She had had the disease of childhood with more than usual severity, repeated attacks of tonsillitis and dysmenorrhea for a long time. She occasionally took aminopyrine for the latter but was uncertain as to the amount. She had recently taken time off from her

TABLE 1.—*E. D., Patient of Dr. M. Simkin*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Segmented Neutrophils, %
5/ 2/34	.....	....	4,000	..	..	..	..	..
5/ 4/34	.....	4.23	2,900	60	..	1	1	38
5/ 5/34	.....	4.57	1,950	64	..	1	1	33
5/ 6/34	a.m.	....	1,500	52	..	..	2	36
	p.m.	....	2,650	54	2	2	..	44
5/ 7/34	.....	....	3,900	55	9	2	1	33
5/ 8/34	.....	....	2,200	52	..	..	..	48
5/ 9/34	.....	....	2,500	49	..	3	1	47
5/10/34	.....	4.02	2,450	59	..	4	..	37
5/11/34	.....	....	2,300	55	..	..	..	44
5/12/34	.....	....	3,400	37	..	..	..	63
5/13/34	.....	....	3,850	22	..	4	..	74
5/14/34	.....	....	4,500	25	..	..	..	75
5/15/34	.....	....	5,050	23	..	1	..	76
5/16/34	.....	....	5,700	23	..	1	..	76
5/17/34	.....	....	6,850	33	..	..	..	67
5/18/34	.....	....	6,350	21	..	..	..	79
5/19/34	.....	3.91	3,950	29	..	..	..	71
5/20/34	.....	....	6,500	..	..	..	..	..
5/21/34	.....	3.42	4,100	17	2	..	..	81
5/22/34	.....	....	4,150	16	..	..	..	84
5/23/34	.....	....	5,450	27	1	..	1	71
5/24/34	.....	....	4,250	27	..	3	..	69
5/25/34	.....	....	4,200	33	..	..	1	61
5/26/34	.....	4.27	4,250	30	..	..	1	71
5/27/34	.....	....	4,500	24	..	..	2	74
5/28/34	.....	....	7,500	..	..	..	..	..
5/31/34	.....	....	6,000	26	1	..	1	72
6/ 2/34	.....	....	6,200	..	..	..	..	..
6/ 3/34	.....	....	6,100	..	..	..	..	..
6/ 4/34	.....	....	5,800	..	..	..	..	..
6/ 7/34	.....	....	6,300	28	..	..	..	72
6/ 9/34	.....	....	6,500	..	..	..	..	..
6/11/34	.....	....	6,000	..	..	..	..	..
6/21/34	.....	....	6,100	..	..	..	..	..
6/23/34	.....	....	5,900	..	..	..	..	..
6/26/34	.....	....	5,600	..	..	..	..	..
6/29/34	.....	....	6,000	26	..	..	..	74
7/ 2/34	.....	....	5,800	..	..	..	..	..
7/ 5/34	.....	....	4,000	..	..	..	..	..
7/ 9/34	.....	....	7,500	..	..	..	..	..
7/12/34	.....	....	6,500	..	..	..	..	..
7/20/34	.....	....	5,900	30	..	..	..	70

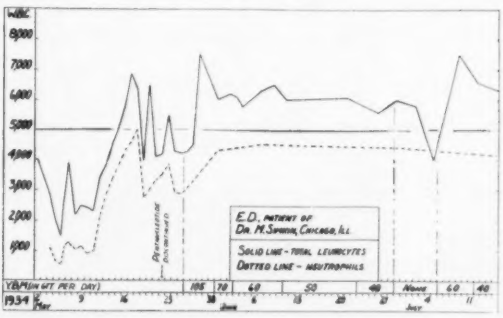
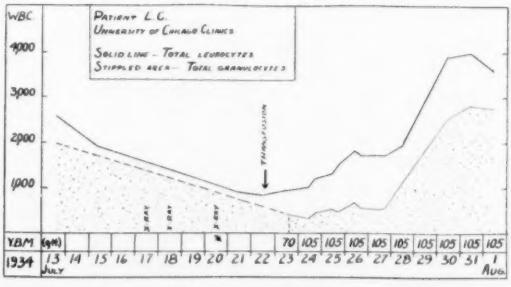


TABLE 2.—*L. C., Patient in University of Chicago Clinics*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils, %		
								Segmented	Metamyelocytes	Myelocytes
1/13/31	.....	5.50	8,800	..	..	..	..	..	..	..
5/15/34	.....	5.20	7,400	..	..	..	..	..	..	..
7/ 3/34	.....	4.37	4,050	..	..	..	..	..	..	..
7/ 9/34	.....	....	3,100	..	..	..	..	..	..	..
7/12/34	.....	3.89	2,500	..	..	..	..	..	..	..
7/13/34	.....	4.40	2,600	17	5	3	1	74	..	..
7/15/34	.....	....	1,900	..	..	..	..	..	..	..
7/21/34	.....	3.90	900	..	..	..	..	..	..	..
7/22/34	.....	5.10	850	..	..	..	..	..	..	..
7/23/34	.....	4.44	950	35	10	2	9	44	..	..
7/24/34	a.m.	....	1,000	52	11	2	3	32	..	..
	p.m.	....	1,200	40	15	4	3	38	..	..
7/25/34	a.m.	....	1,300	40	14	2	3	38	3	..
	p.m.	....	1,500	45	16	2	4	30	2	1
7/26/34	a.m.	....	1,800	38	20	3	1	38	..	..
	p.m.	....	1,700	46	14	5	2	33	..	..
7/27/34	a.m.	....	1,700	45	13	3	2	37	..	..
	p.m.	....	1,700	46	12	3	1	38	..	..
7/28/34	.....	....	1,900	27	12	2	2	57	..	..
7/30/34	.....	....	3,900	25	8	2	..	65	..	..
7/31/34	.....	....	4,000	20	6	2	1	71	..	..
8/ 1/34	.....	4.60	3,600	17	3	3	..	77	..	..



work because of a "run-down and nervous" condition. The basal metabolic rate about a week before her present disturbance was —17; since then she had been taking thyroid.

Physical examination revealed no abnormality except injection of the pharynx, cervical adenopathy and swelling of the right tonsillar area, suggestive of an abscess behind it. The temperature was 103.6 F. A blood count showed: hemoglobin, 64 per cent; erythrocytes, 3,460,000, and leukocytes, 1,000, with 1 per cent neutrophils.

A transfusion was given, and treatment with liver extract and pentnucleotide was begun. She grew steadily worse; on the evening of October 25 the temperature reached 105.6 F. (rectal). The white cell count on October 25 was 1,450 in the morning and 650 in the afternoon. After a transfusion (10 p. m.) there were 1,820 leukocytes. Yellow bone marrow concentrate was given, 5 cc. for the initial dose at 11 p. m., followed by 1.5 cc. every four hours. The use of pentnucleotide and liver was discontinued. On the following day her condition was essentially unchanged; she was irrational at times. There was definite clinical improvement on October 27, with the temperature 102.4 to 104.4 F., and the throat somewhat

less painful. The next day showed continued clinical improvement, the temperature approaching normal and the leukocyte count being approximately doubled (3,800). The count rose rapidly—6,400 on the morning of October 29, 7,200 in the afternoon, 9,850 (54 per cent neutrophils) on the morning of October 30 and 11,250 in the afternoon. A small ulcerated area developed near the right tonsil, and later a small ulcer appeared under the tongue. Pus was draining from around the upper pole of the right tonsil. The throat remained painful until November 6, when a localized abscess on the right side of the neck was opened and drained. The white cell count was about 15,000.

After drainage of the abscess the patient improved rapidly. Treatment with yellow bone marrow concentrate, the dose having been reduced to 0.5 cc. every four hours, was discontinued on November 9 (the eighteenth day). By November 13 the mouth and throat looked normal, and the neck was healed. The white cell count varied between 9,000 and 15,000, with about 45 per cent neutrophils (mostly polymorphonuclears), until her discharge on November 16. The final diagnosis was agranulocytosis (table 3 and chart 3).

CASE 5.—A single woman (a patient of Dr. E. M. Birchwood), an office worker aged 38, came to the office on May 14, 1935, with a complaint of fatigue, sleeplessness and poor appetite. She was unable to do the work she had previously been doing. She had been worrying over illness and death in her family. There was nothing significant in her past history; her general health had been good except for headaches since an infection of the upper respiratory tract in January 1935. There appears no statement in regard to the use of aminopyrine.

Physical examination revealed only a mildly inflamed mouth and pharynx and a coated tongue. The laboratory findings were normal except that the blood count showed: hemoglobin, 80 per cent; erythrocytes, 4,140,000 and leukocytes, 2,800, with 62 per cent polymorphonuclears.

She was asked to return in a week, to allow for completion of laboratory tests. On May 21 the white cell count was unchanged—2,900, with 68 per cent polymorphonuclears. Treatment with yellow bone marrow concentrate was started, 1 cc. three times a day, and she was told to rest in bed. When seen one week later she said she felt much better and was out of bed. The leukocyte count was 3,600, with 67 per cent polymorphonuclears. The dose of yellow bone marrow concentrate was increased to 5 cc. three times a day for one day and then was 5 cc. daily.

When seen on June 4 the patient said she felt well but was somewhat weak. A blood count revealed 7,225 leukocytes, with 72 per cent polymorphonuclears. She returned to work; on June 11 the blood showed 7,600 leukocytes and a normal differential picture. When seen again on June 18 she felt well. As the white cell count was normal (8,200), the use of yellow bone marrow concentrate was discontinued. The further progress was uneventful; the count remained normal.

The diagnosis was chronic leukopenia (table 4 and chart 4).

CASE 6.—Mrs. H. F., a housewife aged 31 (a patient of Dr. D. E. Markson), was admitted to the Norwegian-American Hospital on June 14, 1935, with complaints of malaise, fever and sore throat. She had been well until the past month. About May 15 she had a tonsillectomy; on May 22 an abscessed upper molar was extracted. About June 1 she had sore gums, a temperature of 101 to 103 F., headache and malaise. She was given four injections of neoarsphenamine, but the lesions were not improved by this or by mouth washes. Several pieces of tissue were removed from the floor of the mouth a few days before she entered the hospital. No statement appears regarding the use of aminopyrine.

TABLE 3.—*D. S., Patient of Dr. N. C. Gilbert, St. Luke's Hospital*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Neutrophils, %			Myelocytes, %	Promyelocytes, %
						Segmented	Band Form	Metamyelocytes		
10/23/36	a.m.	3.46	1,000	99.0	...	1.0	....	...	..	...
	p.m.	....	1,350							
10/24/36	.....	3.52	1,050	99.0	1.0	....	....	...	..	...
10/25/36	a.m.	4.04	1,450	96.0	2.0	2.0	....	...	..	...
	p.m.	....	650							
	p.m.	...	1,820							
10/26/36	a.m.	3.80	900	94.0	4.0	2.0	....	...	..	...
			800							
	p.m.	....	1,850							
10/27/36	.....	3.68	2,000	86.0	7.0	4.0	3.0	...	..	...
			1,100							
10/28/36	.....	4.11	3,800	....	...	....	....	...	..	...
10/29/36	a.m.	3.75	6,400	36.0	6.5	24.0	28.0	5.5	..	...
	p.m.	....	7,200							
10/30/36	a.m.	3.92	9,850	43.0	3.0	37.5	14.0	2.5	..	...
	p.m.	....	11,250							
10/31/36	a.m.	3.89	9,000	31.0	3.0	32.5	19.5	8.5	1	4.5
	p.m.	....	7,350							
11/ 1/36	.....	4.00	8,750	36.5	2.5	28.5	22.0	8.0	2	0.5
11/ 2/36	a.m.	....	9,150	....	...	....	....	...	..	...
	p.m.	....	12,550	45.0	4.0	32.0	12.0	4.0	3	
11/ 3/36	a.m.	3.92	10,650	41.0	3.0	35.0	18.0	1.0	2	
	p.m.	....	11,300							
		4.02	12,300	40.0	1.0	52.0	6.0	1.0		
11/ 5/36	a.m.	4.11	17,450	31.0	2.5	57.5	8.0	1.0		
	p.m.	....	18,100							
11/ 6/36	a.m.	4.20	14,550	28.5	2.0	66.0	3.5	...		
	p.m.	....	15,500							
11/ 7/36	a.m.	4.08	12,450	36.0	0.5	62.0	1.5	...		
	p.m.	....	13,400							
11/ 8/36	.....	4.08	11,350	57.0	2.0	39.5	1.5	...		
11/ 9/36	a.m.	4.07	9,850	51.5	1.5	47.0	....	...		
	p.m.	....	9,050							
11/10/36	a.m.	4.00	10,050	55.0	4.0	39.0	1.5	1.5		
11/12/36	p.m.	....	10,250							
	a.m.	4.12	9,400	50.0	4.0	42.5	3.5			
	p.m.	....	11,300							
11/13/36	a.m.	4.09	12,500	55.5	2.5	41.0	2.0			
	p.m.	....	13,250							
11/14/36	a.m.	4.11	14,450	47.0	6.0	47.0	...			
	p.m.	....	12,300							
11/15/36	a.m.	4.21	10,700	51.5	2.5	45.5	1.5			
	p.m.	....	10,600							
11/16/36	a.m.	4.26	13,250	55.0	2.0	43.0				
	p.m.	....	11,200							

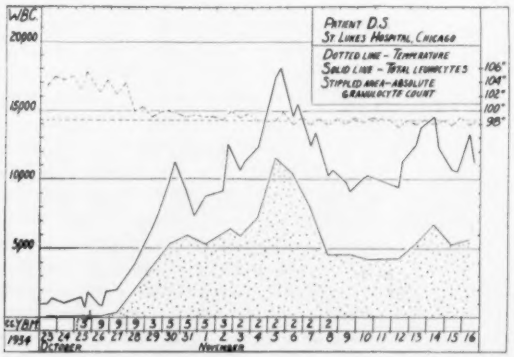
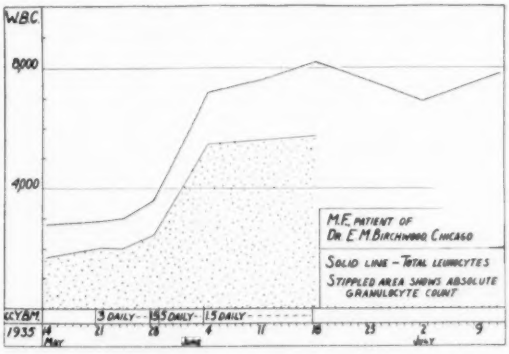


TABLE 4.—*M. F., Patient of Dr. E. M. Birchwood*

Date	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Neutrophils, %	
						Basophils	Segmented
5/14/36	4.14	2,800	35	3	..	..	62
5/21/36	....	2,900	30	..	1	1	68
5/24/36	4.30	3,000	30	3	1	2	64
5/28/36	....	3,600	32	..	1	..	67
6/ 4/36	....	7,225	24	..	4	..	72
6/11/36	4.24	7,600	22	4	2	2	70
6/18/36	....	8,200	30	..	1	1	68
7/ 2/36	....	6,900	..	..	..	..	..
7/12/36	....	7,800	..	..	..	..	..
7/23(?)	4.24	6,425	28	..	1	1	70



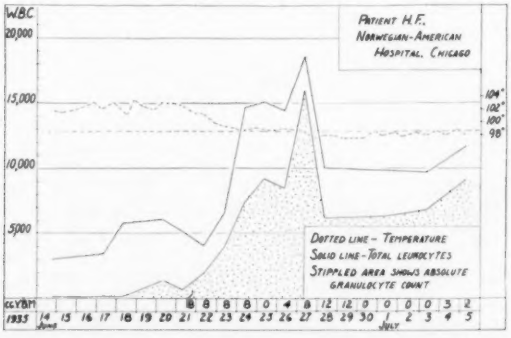
Physical examination revealed an ulcerated area on the left side of the mouth and under the tongue covered with necrotic tissue. The gingival margins were red, the throat was slightly reddened and the temperature was 101.8 F. Other physical findings were normal. The blood count showed: hemoglobin, 85 per cent; erythrocytes, 3,860,000, and leukocytes, 2,850 and 3,250, respectively, on two occasions, with over 90 per cent lymphocytes.

The patient was given pentnucleotide, 10 cc. twice a day, beginning on June 15, but had moderate to severe reactions to the injections, and she protested at the treatment. The leukocyte count rose on June 18 to 20 to about 6,000, with 23 per cent granulocytes, but fell again on the two following days. The oral lesions were extending, and the clinical picture was essentially unchanged. On June 21 the white cell count was 5,100, with 15 per cent polymorphonuclears. Treatment with pentnucleotide was discontinued, and yellow bone marrow concentrate was given, beginning with 5 cc. at 6 p. m. On the following day the temperature fell below 100 F. for the first time, and the granulocyte count rose to 50 per cent.

On June 23 (forty hours after treatment with yellow bone marrow concentrate was begun) the leukocyte count was 6,600, with 59 per cent neutrophils. The general condition was improved. Twenty-four hours later there were 14,650 leukocytes, with 50 per cent polymorphonuclears, and the temperature was normal. The ulcer in the floor of the mouth, which had extended to the gum between the lower incisors on the left, began to show resolution. A slough was forming on the left side of the upper gingival margin where the tooth was extracted. The

TABLE 5.—*H. F., Patient of Dr. D. E. Markson, Norwegian-American Hospital*

Date	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Eosinophils, %	Segmented Neutrophils, %	Unclassified
6/14/35	3.86	3,250	90	..	1	9
		2,850	94	..	2	4
6/16/35	....	3,350	96	..	0	4
6/17/35	....	3,400	70	..	1	29
6/18/35	....	7,300	50	..	1	49
		4,250	53	..	0	47
6/20/35	3.84	6,060	76	1	12	11
6/21/35	....	5,100	48	..	14	38
6/22/35	....	4,050	50	9	39	2
6/23/35	....	6,600	32	..	53	15
6/24/35	....	14,650	30	..	50	20
6/25/35	....	15,050	36	..	56	8
6/26/35	....	14,350	36	..	59	5
6/27/35	4.96	18,650	11	..	80	9
6/28/35	....	10,050	35	..	61	4
7/ 1/35	....	9,800	32	..	64	4
7/ 3/35	....	9,650	30	..	69	1
7/ 5/35	....	11,700	23	..	77	



dose of yellow bone marrow concentrate was changed to 4 cc. three times a day. The leukocyte count continued at a high level (14,000 to 18,000) until June 28, when it was 10,050, with 61 per cent polymorphonuclears. The temperature was normal, the clinical condition was good and the infection in the mouth was definitely arrested. The gums were pink.

On July 2 necrotic tissue had come away, revealing the great depth of the ulcer; the posterior aspects of the roots of the incisors were visible almost to their tips. The patient's condition was steadily improving. The dose of yellow bone marrow concentrate was reduced to 1 cc. twice a day for two days and was then discontinued. The patient returned to her home on July 5. The blood picture since then has been normal, and the oral lesions are entirely healed.

The diagnosis was agranulocytosis (table 5 and chart 5).

CASE 7.—Mrs. E. S., a housewife aged 32 (a patient of Dr. T. E. Walsh), was admitted to the Billings Hospital, University of Chicago Clinics, on April 3, 1936, complaining of sore throat, fever, bleeding from the mouth, deafness and diarrhea. She had had the sore throat for two weeks and had been given aminopyrine and allonal (allylisopropylbarbituric acid with aminopyrine) by another physician. The deafness, bleeding and diarrhea were of a few days' duration. She had had no other illness.

Physical examination revealed ulceration and bleeding in the gingivolabial fold on both sides of the upper jaw. The tonsils were swollen and ulcerated and the left one was bleeding; the odor was foul. The posterior wall of the pharynx was covered with a blood clot. The patient could not hear the spoken voice. The temperature was 105 F. A blood count showed: erythrocytes, 3,200,000, and leukocytes, 800 to 1,000; no granulocytes were seen.

The patient was given a transfusion of 550 cc. of citrated blood, and treatment with yellow bone marrow concentrate was begun, with 5 cc. every four hours for twenty-four hours, then 5 cc. four times a day. Pentnucleotide also was given, 20 cc. twice a day. There was little change on the following day, but on April 5 the leukocyte count rose from 1,600 at 10 a. m. to 4,800 at 10 p. m., with many immature granulocytes. A transfusion of 550 cc. of citrated blood at 8 p. m. may have contributed slightly to this rise. The patient seemed somewhat better clinically. On April 6 the blood picture was much improved: 9,700 leukocytes at 10:30 a. m., with 85 per cent neutrophils, mostly immature; 11,400 at 5 p. m., with 79 per cent neutrophils, of which 58 per cent were polymorphonuclears. The dose of yellow bone marrow was reduced to 2 cc. four times a day, and the dose of pentnucleotide was reduced to 10 cc. twice a day (omitted on April 8).

By April 7 the count had risen to 19,400, with 79 per cent neutrophils. Bleeding had stopped, even on removal of necrotic sloughs. The left side of the superior maxilla was denuded and showed some necrosis. The general condition was definitely better, the temperature approaching normal. Treatment with pentnucleotide was discontinued on April 11. By April 12 the leukocyte count was 30,000, with 88 per cent neutrophils, and the temperature was normal. The patient felt much better and could hear the spoken voice. The use of yellow bone marrow concentrate was discontinued on April 14. The leukocyte count fell to 18,100 on April 15.

The general condition improved steadily, and the patient was discharged on April 25. On May 28, when two molars and a sequestrum were removed from the left side of the upper jaw, the leukocyte count was 9,000, with 57 per cent polymorphonuclears.

The diagnosis was agranulocytic angina (table 6 and chart 6).

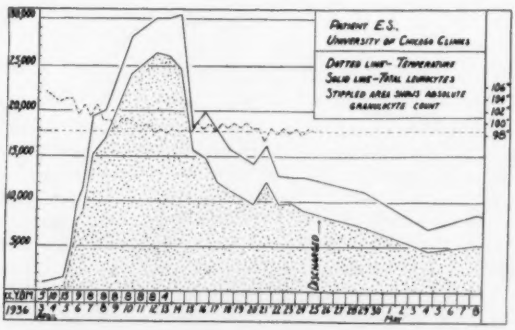
Case 8.—A woman office worker aged 29 (a patient of Dr. E. R. Stoehr) complained on April 20, 1936, of weakness, susceptibility to fatigue, a noticeable lack of vigor and also a severe local and systemic reaction to smallpox vaccination (given April 10). She had been ill for six months with a condition characterized by deficiency of the leukocytes six years previously. This was said to follow obstinate ulcerations resulting from superficial injuries. The patient had periods of extreme nervous irritability, periodic migraine and occasional insomnia. No statement appears regarding the use of aminopyrine.

Physical examination showed that the tonsils were red and partly covered with a gray deposit. There was slight cervical adenopathy, and the splenic area was slightly tender. The blood count showed: erythrocytes, 4,750,000, and leukocytes, 3,650, with 10 per cent lymphocytes, 9 per cent monocytes, 4 per cent band cells and 77 per cent mature neutrophils.

The patient returned the following day (April 21), and the leukocyte count was 3,300, with 63 per cent neutrophils. Yellow bone marrow concentrate was given in 2.5 cc. doses at four hour intervals for four doses. The leukocyte count on the morning of April 22 was 4,800, with 67 per cent neutrophils and 20 per cent monocytes. Three 2.5 cc. doses of yellow bone marrow concentrate were given. At 6:30 p. m. she had an attack of cyanosis, which was relieved by dextrose and insulin. At 11 p. m. there were 7,300 leukocytes.

TABLE 6.—*E. S., Patient of Dr. T. E. Walsh, University of Chicago Clinics*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils, %			Myelocytes, %	Promyelocytes, %	Myeloblasts, %	Plasma Cells, %
								Segmented	Band Form	Metamyelocytes				
4/ 3/36	p.m.	3.20	1,000	100.0										
4/ 4/36	a.m.	....	1,300											
	p.m.	....	1,400											
4/ 5/36	a.m.	....	1,600											
	p.m.	....	4,800					Many immature granulocytes						
4/ 6/36	a.m.	....	9,700	12.0	3.0	...	..	22.0	14.00	21.00	2.0	23.0	3	
	p.m.	....	11,400	20.0	1.0	...	..	58.0	.....	4.00	15.0	....	..	2
4/ 7/36		3.25	19,400	9.0	12.0	...	..	53.0	8.00	7.00	....	3.0	1	
4/ 8/36		....	20,000	8.0	7.0	...	..	44.0	15.00	8.00	17.0	....	1	
4/10/36		....	28,000	7.0	6.0	...	..	30.0	26.00	20.00	10.0	....	1	
4/12/36		....	30,000	12.0	....	...	..	27.0	17.00	34.00	10.0	....	1	
4/13/36		....	30,000	13.0	....	...	..	49.0	2.00	36.00	....	....		
4/14/36		....	30,400	16.0	2.0	...	..	58.0	5.00	18.00	....	....		
4/15/36		3.30	18,100	13.0	....	...	..	60.0	4.00	16.00	1.0	....		
4/16/36		....	19,900	21.0	4.0	...	..	54.0	5.00	14.00	2.0	....		
4/17/36		....	17,800	21.0	11.0	1.0	..	58.0	.....	9.00	....	....		
4/18/36		....	15,800	21.0	7.5	0.5	..	64.5	.....	6.00	0.5	....		
4/20/36		....	14,100	24.5	7.0	1.0	..	65.5	.....	2.00	....	....		
4/21/36		....	16,200	17.0	8.0	1.0	..	73.2	0.80	.....	....	....		
4/22/36		3.53	12,900	18.5	6.5	2.5	..	70.5	0.25	1.75	....	....		
4/23/36		....	12,700	17.0	6.0	2.5	..	74.5	.....	.....	....	....		
4/24/36		....	12,700	23.5	6.0	2.0	..	68.5	.....	.....	....	....		
4/29/36		....	11,000	27.0	7.0	0.5	2	63.0	.....	.....	....	0.5		
5/ 4/36		....	7,000	35.0	10.0	...	..	55.0						
5/ 8/36		....	8,500	32.0	4.0	...	..	62.0						
5/14/36		....	7,400	27.0	10.0	1.0	1	60.0						



On April 23 the leukocyte count reached its maximum, 11,400, with 76 per cent segmented neutrophils. This was an increase of over 200 per cent in the forty-four hours since the administration of the initial dose of yellow bone marrow concentrate. The subsequent course was uneventful. Yellow bone marrow concentrate was given in doses up to 24 drops daily and finally was discontinued.

The diagnosis was leukopenia (table 7 and chart 7).

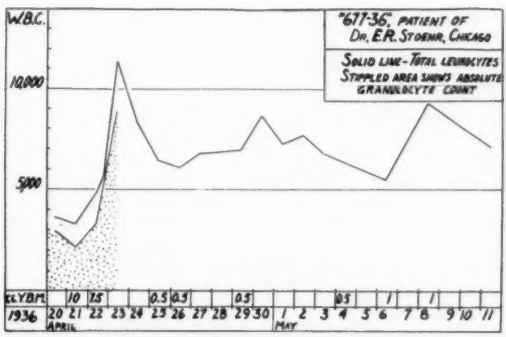
CASE 9.—Miss P. M., aged 37 (a patient of Drs. P. E. Hopkins and W. W. Sittler), was admitted to the Evangelical Hospital on June 26, 1936, because of sore throat, malaise and fever. She had been in good health until May 1, when

sore throat and mild fever developed. This condition persisted for about three weeks. On June 22 she again had a sore throat, with a chill and general aching. By June 25 both tonsils were red, with necrotic spots; there were necrotic spots on the gums also.

Physical examination revealed nothing abnormal outside the mouth and throat. "Necrotic areas were noted in the crypts of both tonsils, and a white thin mem-

TABLE 7.—*Patient of Dr. E. R. Stoehr*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Eosinophils, %	Basophils, %	Neutrophils, %	
								Segmented	Band Form
4/20/36	.....	4.75	3,650	10	9	..	..	77	4
4/21/36	.....	....	3,300	6	14	..	2	57	6
4/22/36	10 a.m.	....	4,800	12	20	..	1	62	5
	8 p.m.	....	5,750	..	..	..	..	..	..
	11 p.m.	....	7,300	..	..	..	..	..	..
4/23/36	8 a.m.	....	11,400	15	6	2	..	76	..

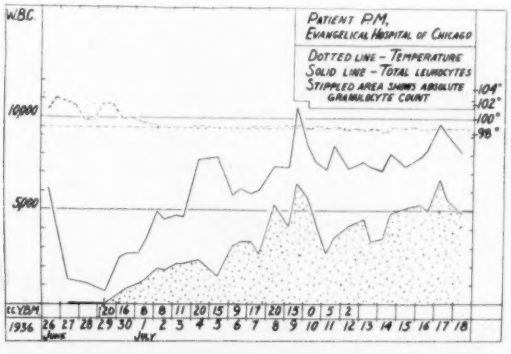


brane was noted over the anterior right pillar and on the left posterior pharyngeal wall. There was an inflammatory area about the membrane extending over the anterior pillars and the uvula. Small necrotic areas also appeared in the gingival margins of several teeth." The submaxillary lymph nodes were moderately enlarged. The blood count at the time of entry was not significant—erythrocytes, 3,760,000; hemoglobin, 75 per cent, and leukocytes, 6,150. No differential count was made.

Treatment was largely palliative for the first two days; 60 cc. of nonspecific human serum, 10 grains (0.65 Gm.) of aminopyrine and 2 cc. of liver extract parenterally were given in addition. The lesions were somewhat improved on the second day, but the leukocyte count had fallen to 1,300, with 98 per cent lymphocytes. On June 28 the leukocyte count was 1,100, the patient was weak and the lesions had spread to the uvula. Pentnucleotide was given, 10 cc. twice a day. On the fourth day (June 29) the leukocyte count had dropped to 650, with 1 per cent band cells and 99 per cent lymphocytes. The uvula was swollen to twice its normal size and was covered with membrane; the tonsils were very red and partly covered with membrane. The temperature was 101.8 F. Yellow bone marrow concentrate was ordered, 5 cc. every four hours for twenty-four hours and then 2 cc. four times a day.

TABLE 8.—*P. M., Patient of Drs. P. E. Hopkins and W. W. Sittler, Evangelical Hospital of Chicago*

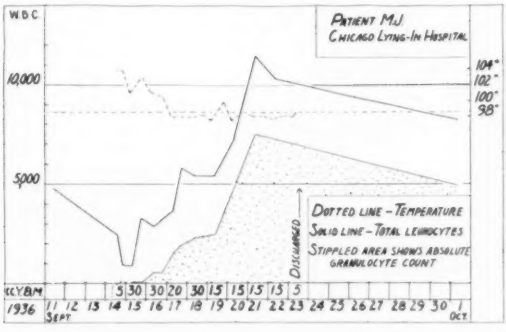
Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Basophils, %	Neutrophils, %			Myelocytes, %	Plasma Cells, %
							Segmented	Band Form	Metamyelocytes		
6/26/36		3.76	6,150	..	..	..	..	..	..	..	..
6/27/36		3.61	1,300	98	..	..	..	1	1	..	..
6/28/36		4.05	1,100	..	..	..	..	..	..	..	..
6/29/36		....	650	99	..	..	..	1	..	..	..
6/30/36	a.m.	....	2,450	74	..	..	2	12	8	2	2
	p.m.	3.71	2,650	59	8	..	24	..	6	3	..
7/ 1/36	a.m.	3.82	2,650	60	..	..	27	7	3	..	..
	p.m.	3.96	3,400	58	3	..	19	16	4	..	..
7/ 2/36	a.m.	4.08	4,900	60	1	..	13	21	3	1	1
	p.m.	3.71	4,500	60	..	..	15	11	10	4	..
7/ 3/36	a.m.	4.00	4,700	64	..	..	12	16	5	1	1
	p.m.	4.07	4,650	64	..	..	16	12	6	2	..
7/ 4/36		4.10	7,700	69	..	..	20	6	4	1	..
7/ 5/36		4.12	7,850	81	..	..	..	3	16	..	..
7/ 6/36	a.m.	4.12	5,800	48	..	..	47	5	..	..	..
	p.m.	4.075	6,100	46	3	..	48	3	..	..	..
7/ 7/36	a.m.	4.15	5,900	39	4	..	54	3	..	..	..
	p.m.	3.99	6,050	49	7	..	40	4	..	..	..
		4.20	7,350	28	4	..	64	4	..	..	..
7/ 9/36	a.m.	4.29	7,300	38	3	..	54	3	1	..	2
	p.m.	4.13	10,600	38	1	..	31	29	..	..	..
7/10/36	a.m.	4.25	8,400	31	..	..	47	16	3	..	1
	p.m.	4.25	7,650	40	..	..	35	20	4	2	1
7/11/36	a.m.	4.21	7,200	60	2	..	30	8	..	..	
	p.m.	4.45	8,500	58	..	..	24	16	2	..	
7/12/36	a.m.	4.26	7,250	42	..	..	28	20	6	4	
7/13/36	a.m.	4.15	7,600	40	..	..	28	28	4	..	
	p.m.	4.45	7,350	52	2	..	24	18	2	2	
7/14/36	a.m.	4.30	7,150	50	..	..	42	6	1	..	
	p.m.	4.22	8,050	40	..	1	27	14	10	8	
7/15/36		4.16	7,350	30	..	1	27	32	6	4	
7/16/36	a.m.	4.25	7,900	32	..	..	48	14	4	2	
	p.m.	4.10	8,350	40	..	..	42	8	4	6	
7/17/36	a.m.	4.40	9,700	30	..	1	51	18	..	..	
	p.m.	4.27	9,100	38	..	..	38	10	10	4	
7/18/36		4.35	8,100	40	..	2	42	10	4	2	



On June 30 the white cell count in the morning was 2,450, with 24 per cent neutrophils, and had risen by evening to 2,650, with 33 per cent neutrophils, mostly segmented. The condition of the throat was greatly improved, much of the membrane having disappeared. The temperature fell below 100 F.; the general condition

TABLE 9.—*M. J., Patient in Chicago Lying-In Hospital*

Date	Time	Erythrocytes, Million	Leukocytes	Lymphocytes, %	Monocytes, %	Basophils, %	Neutrophils, %			
							Segmented	Band Form	Metamyelocytes	Myelocytes, %
9/11/36	.....	....	4,800	....	....	...	....	....	...	...
9/14/36	5 p.m.	....	2,400	....	....	...	....	....	...	...
	10 p.m.	....	925	....	....	...	....	....	...	...
9/15/36	a.m.	4.32	1,000	90.0	7.0	...	3.0	....	...	...
	p.m.	....	3,300	83.0	12.0	...	2.0	2.0	1.0	...
9/16/36	a.m.	....	2,900	70.0	11.0	...	6.0	10.0	2.0	1.0
	p.m.	....	3,200	76.0	7.0	...	3.0	9.0	4.0	1.0
9/17/36	a.m.	....	3,700	51.0	6.5	...	17.0	14.5	5.5	5.0
	p.m.	....	5,800	62.0	4.5	...	8.0	14.0	9.0	2.5
9/18/36	.....	....	5,400	52.0	6.5	...	16.5	13.0	7.0	5.0
9/19/36	.....	....	5,400	50.5	5.0	0.5	34.0	4.0	4.0	2.0
9/21/36	.....	....	11,500	31.0	4.0	...	52.0	12.0	0.5	0.5
9/22/36	.....	....	10,300	28.0	2.0	...	62.0	8.0		
10/ 1/36	.....	4.12	8,200	35.0	5.0	...	60.0			
11/20/36	.....	4.98	6,400	33.0	12.0	...	54.0			



was better. The clincal and hematologic pictures continued to improve. The dose of pentnucleotide was reduced to 10 cc. daily on July 2. There was an abrupt increase in the absolute lymphocyte count on July 4, but this was followed shortly afterward by a corresponding rise in the granulocyte count.

On July 9 the leukocyte count reached 10,600, with 61 per cent neutrophils. Treatment with yellow bone marrow concentrate and pentnucleotide was discontinued. There was an abrupt fall in the total leukocyte and granulocyte counts—7,200 leukocytes, with 38 per cent neutrophils, on July 11. Yellow bone marrow concentrate was given, 5 cc. daily on July 11 and 12. The neutrophil count rose immediately to 58 to 60 per cent. With the use of bone marrow concentrate again discontinued, the neutrophil count again fell below 50 per cent. The blood picture returned to normal shortly, and the patient was discharged in good condition on July 18. The subsequent course was uneventful.

The diagnosis was agranulocytic angina (table 8 and chart 8).

CASE 10.—Mrs. M. J., aged 41, had attended the outpatient clinic of the Chicago Lying-In Hospital. She was admitted to the hospital on Sept. 14, 1936, with acute tonsillitis and pharyngitis and a temperature of 104 F.

In the past she had had an appendectomy, excision of the left ovary, gastric ulcer and gonorrhea. She had had dysmenorrhea, menorrhagia and probably chronic pelvic inflammation for a long time. She was seen in the outpatient

department on September 11 because of vaginal bleeding of ten days' duration. She had been taking a proprietary preparation containing aminopyrine for menstrual pain. The blood picture at that visit showed: cell volume, 41 per cent; hemoglobin, 14.8 Gm., and leukocytes, 4,800.

Physical examination revealed pronounced dark redness of the lateral pharyngeal walls and tonsillar pillars, but no ulceration or membrane. When examined three days previously the throat had been normal. Other findings were normal except for the gynecologic conditions, which probably were not connected with the present illness.

On September 14, the day of entry, the leukocyte count was 2,400 at 5 p. m. and 925 at 10 p. m. Treatment with yellow bone marrow concentrate was started immediately, 5 cc. every four hours. No other hematopoietic stimulant was given. The throat showed little change on the following day; there were small necrotic patches on each tonsil. In the morning the leukocyte count was 1,000, with 90 per cent lymphocytes, 7 per cent monocytes and 3 per cent polymorphonuclear neutrophils. By evening there were 3,300 leukocytes, with little change in the differential picture. On September 16 the patient was improved; the throat looked and felt better and the temperature was falling. The neutrophil count had increased to 19 per cent of 2,900 leukocytes.

There was marked improvement on September 17; in the morning the blood count showed 3,700 leukocytes, with 5 per cent myelocytes, 5.5 per cent metamyelocytes, 14.5 per cent band cells and 17 per cent segmented neutrophils. In the evening the leukocyte count was 5,800, with 33.5 per cent neutrophils. The temperature was normal. The clinical and blood pictures continued to improve. The dose of yellow bone marrow concentrate was reduced to 5 cc. three times a day on September 19. On September 21 the leukocyte count reached its maximum —11,500, with 65 per cent neutrophils, of which 52 per cent were segmented, 12 per cent were band cells and 1 per cent were myelocytes and metamyelocytes.

The patient was discharged in good condition on September 23. Subsequent counts on October 1 and November 21 were within normal limits.

The diagnosis was agranulocytic angina (table 9 and chart 9).

COMMENT

Yellow bone marrow concentrate was used without success in seven cases of leukopenia, not true agranulocytosis. One patient, a woman aged 76 with diabetes of five years' standing, was treated at the University of Chicago Clinics for agranulocytosis (without angina) and abdominal pain. She was given yellow bone marrow concentrate and there was some evidence of myeloid activity after sixty hours, but she died on the sixth day of hospitalization without significant improvement in the blood picture. At autopsy the appendix showed necrotic ulcers, with serofibrinous periappendicitis and mononuclear cell infiltrations without polymorphonuclear response.

In three of these cases the diagnosis was aplastic anemia. Death occurred in the case of a man aged 65 and that of a 5 year old girl, in her case the etiologic factor being obscure. In the third patient, a woman of 35, the condition developed after antisyphilitic treatment, but she ultimately recovered. In none of these three cases was there evidence of

hematopoiesis as a result of treatment with yellow bone marrow. In the other three cases, in which the tentative diagnosis was leukemia, there was no response to the administration of the concentrate.

In cases of acute agranulocytic angina (malignant neutropenia) the condition of the patient is often so critical that any or every hopeful therapy is started, e. g., blood transfusion and the use of sodium pentnucleotide, liver extract and normal or immune serums. Transfusion has been considered to be of transitory value, if any.[13] Jackson and Parker [13] reported beneficial results after the parenteral administration of sodium pentnucleotide and observed that the response of the white blood cells follows four to six days after the beginning of treatment. Liver extract is frequently given, but aside from its bolstering effect on erythropoiesis, it is of doubtful value.[14] Consequently for our six patients with acute agranulocytosis, yellow bone marrow concentrate was used as the sole granulocytopoietic medication in one case and coincidently with pentnucleotide in two cases. In three cases treatment with pentnucleotide was discontinued, and yellow bone marrow concentrate was given after two to sixteen days.

Summary of the Data.—Case 1: The leukocyte count more than doubled in nine days while the patient was given yellow bone marrow concentrate.

Case 2: This patient with acute agranulocytic angina did not show a definite increase in the total leukocyte and granular leukocyte counts until eight days after treatment with pentnucleotide was begun. After the initial rise the total white cell count was not maintained above 5,000. Clinical recovery was slow; about sixteen days elapsed before there was definite resolution of the ulcers, as compared with the rapid recovery in the cases in which yellow bone marrow concentrate was given. In this case the leukocyte count rose from 4,250 to 7,500 forty-eight hours after the use of yellow bone marrow concentrate was begun. The level was maintained at 6,000 for four weeks. Seven days after the concentrate was withdrawn the count had fallen to 4,000, but seventy-two hours after the readministration of yellow bone marrow concentrate it rose again to 7,500. These two responses to marrow therapy, together with the patient's immediate recovery from an attack in 1937, point to active stimulation of the hematopoietic system by the unsaponifiable residue.

Case 3: This patient showed a fourfold increase in the leukocyte count during eight days of treatment with yellow bone marrow concentrate. The differential picture changed from 44 to 71 per cent neutro-

13. Jackson, H., and Parker, F.: Agranulocytosis: Its Etiology and Treatment, New England J. Med. **212**:137 (Jan. 24) 1935.

14. Reich, C., and Reich, E.: Further Studies in the Treatment of Agranulocytosis, J. Lab. & Clin. Med. **22**:503 (Feb.) 1937.

phils. It would be difficult to interpret this as a response to the discontinuation of roentgen treatment, since in the eight day period from July 9 to 17 when roentgen therapy was not given there was no evidence of hematologic recovery.

Case 4: Pentnucleotide and liver extract were used for two days without apparent benefit; forty-eight hours after their use was discontinued and bone marrow therapy was instituted there was an abrupt and sustained rise in the leukocyte count, followed by clinical recovery of the patient. In this patient, as in the others with a febrile condition, the temperature approached normal as the leukocyte count rose to or above a normal level.

Case 5: This patient with chronic leukopenia gave a definite response (100 per cent increase) when the dose of yellow bone marrow concentrate was increased from 1 cc. three times a day to 5 cc. three times a day and then was reduced to 5 cc. daily. Her condition after three weeks of treatment was improved to the point that the blood count was normal and she returned to work.

Case 6: Seven days of treatment with pentnucleotide produced no clinical improvement; the rise in the leukocyte count on the fifth to seventh days was not sustained on the eighth and ninth. Pentnucleotide therapy was discontinued, and yellow bone marrow was given; forty hours later the leukocyte count was 6,600, with 53 per cent neutrophils. The patient's reactions to the parenteral administration of pentnucleotide were so severe that she was at the point of refusing further injections. The prolonged period of granulocytopenia (June 14 to 21) during treatment with pentnucleotide evidently permitted the extension of the ulcerated areas, which later became necrotic.

Case 7: Both yellow bone marrow and pentnucleotide were given from the first day of hospitalization. Here again the leukocyte response in forty-eight hours was marked and sustained, in contrast with the four to six day response to pentnucleotide when given alone.

Case 8: In this case, as in case 5, the differential count was normal, but there was an absolute depression of all leukocytic elements. The white cell count rose from 3,300 to 11,400 in forty-four hours.

Case 9: Twenty-four hours after the initial dose of yellow bone marrow concentrate the leukocyte count had risen from 650 to 2,650; as this was only forty-eight hours after the beginning of pentnucleotide treatment, it seems permissible to ascribe the response to the yellow bone marrow therapy. Of special interest is the decrease in the granulocyte count after the discontinuance of treatment with pentnucleotide and yellow bone marrow concentrate on July 9, with the increase in the granulocyte count when bone marrow concentrate was given again two days later (chart 8).

Case 10: This patient received yellow bone marrow concentrate only. The leukocyte response came twenty-four to thirty-six hours after the beginning of treatment; clinical improvement was evidenced by the following day, and the patient made an uneventful recovery.

SUMMARY AND CONCLUSIONS

Four patients with leukopenia and six with agranulocytic angina (malignant neutropenia),[15] all women, were treated with yellow bone marrow concentrate per os; all recovered. Those with acute leukopenia showed clinical and hematologic improvement at the end of forty to forty-eight hours as a rule. The initial rise continued to the level which might be expected from the nature of the local lesions, and in no case was there a recurrence of the depression of the blood cells or clinical symptoms during the period of treatment. Although it was not always possible to use the yellow bone marrow concentrate alone, the evidence indicates that it has granulocytopoietic activity sufficient to bring about a normal blood picture when used in cases of agranulocytic angina and of some other leukopenias. Whether used alone or jointly with other medication it usually causes a response in forty to forty-eight hours; the interval when sodium pentnucleotide is used is stated to be four to six days. The case of agranulocytosis in which there was no response to therapy with yellow bone marrow was of such a nature (age and complications) as not to invalidate our other findings.

From these clinical tests it is concluded that the yellow bone marrow concentrate contains a substance or substances which act to stimulate the maturation or liberation of leukocytes of the granulocyte series. Clinical recovery in cases of leukopenia or agranulocytic angina coincides with or follows immediately after the restoration of a blood picture consistent with the severity of the local lesions. These results confirm the fundamental clinical observations of Dr. Watkins made on patients treated with whole yellow bone marrow. They establish the activity of a concentrate devoid of the bulky inert neutral fats which make whole bone marrow unpleasant for clinical use.

Armour & Co. gave the fellowship which made this work possible and supplied some of the materials used. A number of physicians cooperated by affording us the opportunity to make clinical tests.

15. Since this paper was written another patient with agranulocytic angina (following the use of aminopyrine), a man of 41, has been treated with yellow bone marrow concentrate and pentnucleotide, with hematologic recovery.

VARIATION IN CREATINE CONTENT OF HUMAN CARDIAC AND VOLUNTARY MUSCLE AT AUTOPSY

CHARLES R. LINEGAR, PH.D.
WASHINGTON, D. C.

THOMAS T. FROST, M.D.
WINSTON-SALEM, N. C.
AND
VICTOR C. MYERS, PH.D., D.SC.
CLEVELAND

The discovery of phosphocreatine and of the part played by this complex in muscular contraction has brought to light one of the major functions of creatine. It appears that the breakdown of phosphocreatine furnishes energy for the contraction,[1] that the amount of breakdown is concerned with the excitability of the muscle [2] and that this compound also acts as a buffer in the chemical reactions of the muscular processes.[3]

Submitted for publication, July 29, 1937.

Aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Biochemistry and the Department of Pathology (City Hospital Division), School of Medicine, Western Reserve University, Cleveland.

A report of this work was presented before the Cleveland Section of the Society for Experimental Biology and Medicine, March 8, 1935 (Linegar, C. R., and Myers, V. C.: Further Studies on the Creatine Content of Heart Muscle, Proc. Soc. Exper. Biol. & Med. **32**:1016, 1935).

1. (*a*) Rose, W. C.: The Metabolism of Creatine and Creatinine, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1933, vol. 2, p. 187. (*b*) An important paper bearing on the role of phosphocreatine in the activity of the heart (Burns, W., and Cruickshank, E. W. H.: Changes in Creatine, Phosphagen and Adenylpyrophosphate in Relation to the Gaseous Metabolism of the Heart, J. Physiol. **91**:314 [Dec. 14] 1937) appeared while the proof on the present article was being read. Burns and Cruickshank investigated the relation between phosphagen (phosphocreatine) and adenylpyrophosphate in the mammalian heart and found that in the excised heart of the cat arrested in certain stages of asphyxia loss of phosphagen preceded that of adenylpyrophosphate and in complete asphyxia the loss was approximately 80 and 60 per cent, respectively, for phosphagen and adenylpyrophosphate. Similar results were obtained with the dog's heart. Fatigue in the presence of oxygen, on the other hand, produced no great loss of phosphagen, although the loss of adenylpyrophosphate was considerably more than that of phosphagen, the loss in the ventricle being 25 per cent for phosphagen and 50 per cent for adenylpyrophosphate.

2. Needham, D. M.: The Biochemistry of Muscle, London, Methuen & Co., Ltd., 1932.

3. Fiske, C. H., and Subbarow, Y.: Phosphocreatine, J. Biol. Chem. **81**:629, 1929.

Various but unfruitful attempts have been made to ascribe to creatine functions other than its role in muscular contraction. Since creatine is universally present in high concentration in muscle of vertebrates, it is logical to assume that it is an important constituent. Its concentration apparently depends somewhat on the function and efficiency of the muscle,[4] since voluntary muscle contains the highest and smooth muscle the lowest concentration and in certain species white muscle contains more creatine than red muscle.

Although there are many reports on variations in the creatine content of muscles of animals,[4] a surprisingly small number of observations have been reported on the creatine content of skeletal and cardiac muscles of the human subject.

The first analyses of normal and pathologic human skeletal muscle were made by Chisolm[5] in 1912, but in the light of more recent data his creatine values were too low, presumably because of the method used or possibly because of postmortem factors. One year later Myers and Fine[6] reported three creatine analyses of human leg and abdominal muscles. In 1914 Shaffer[7] found a somewhat decreased creatine content of muscle in 2 patients with diabetes and in 1 patient who died of exophthalmic goiter and in whom muscular efficiency was lowered. Denis,[8] in 1916, confirmed and extended these findings by making determinations of the creatine content of the psoas muscles of 5 normal persons and 70 patients dying of acute and chronic diseases. She found that for most patients dying of acute diseases the muscle gave normal figures for creatine and that for others, particularly those dying of septicemia, there was a marked reduction in the creatine content. For those patients who had been in a cachectic condition for several weeks or months before death and who were greatly emaciated, the creatine content of the muscles was reduced both absolutely and relatively, but for the others the creatine value was not decreased.

For 1 patient with generalized myositis fibrosa, a disease involving the muscular system, Bodansky, Schwab and Brindley[9] reported a low creatine content, which varied from 160 to 324 mg. per hundred grams

4. Hunter, A.: Creatine and Creatinine, New York, Longmans, Green & Company, 1928.

5. Chisolm, R. A.: The Creatine Content of Muscle in Malignant Disease and Other Pathological Conditions, Biochem. J. **6**:243, 1912.

6. Myers, V. C., and Fine, M. S.: The Creatine Content of Muscle Under Normal Conditions: Its Relation to the Urinary Creatinine, J. Biol. Chem. **14**:9, 1913.

7. Shaffer, P. A.: Observations on Creatine and Creatinine, J. Biol. Chem. **18**:525, 1914.

8. Denis, W.: Creatine in Human Muscle, J. Biol. Chem. **26**:379, 1916.

9. Bodansky, M.; Schwab, E. H., and Brindley, P.: Creatine Metabolism in a Case of Generalized Myositis Fibrosa, J. Biol. Chem. **85**:307, 1929-1930.

of muscle, in 9 different muscles. They found that in this disease there is an inability to retain exogenous creatine, and they suggested that the inflammation interferes with the normal storage of creatine. Bodansky [10] presented analyses of various muscles of 3 normal persons who had died as the result of accidents and showed that the creatine concentration of the pectoralis major muscle, for example, varied from 433 to 484 mg. A severe disturbance of creatine metabolism was observed by Steinitz and Steinfeld [11] in a patient with dermatomyositis who was investigated for a considerable period. The individual muscles showed a lowered creatine content, which the authors claimed was referable to anatomic changes in the musculature.

The first figures on the creatine content of human cardiac muscle were reported by Constabel,[12] who gave a range of 170 to 180 mg. for normal persons and 70 to 188 mg. for patients with pathologic conditions. In Bodansky's [10] 3 normal persons the creatine concentration, presumably of the muscle of the left ventricle, varied from 220 to 285 mg. In 1929 Vollmer [13] found a concentration of 143 mg. of creatine in the cardiac muscle of an old man who had fatty degeneration of the heart. Cowan [14] reported a normal range, from 117 to 264 mg., of creatine (comparable creatine, based on an 80 per cent water content) for the left ventricle of 48 supposedly normal persons, the arithmetical mean being 194 ± 33 mg. He stated that this group included persons who showed no clinical symptoms or marked gross or microscopic anatomic changes but that in many cases the heart could not be considered perfectly normal from an anatomic point of view. In 17 patients with heart failure he found the average creatine content of the left ventricle to be 144 mg., which was 50 mg. (25.8 per cent lower) than that for his group of normal persons, but the cardiac creatine content of 6 of these patients fell within the normal range. The range for comparable creatine in his group of patients with miscellaneous disorders was from 68 to 208 mg., with a mean of 165 ± 30 mg. He found that septicemia did not reduce the creatine content, and the effect of hypertrophy was not definitely established, although there is a possibility that the hypertrophied heart has a higher creatine content than the nonhypertrophied

10. Bodansky, M.: Creatine in Human Muscle, J. Biol. Chem. **91**:147, 1931.

11. Steinitz, H., and Steinfeld, F.: Untersuchungen zum Kreatinstoffwechsel bei Dermatomyositis, Ztschr. f. d. ges. exper. Med. **79**:319, 1931.

12. Constabel, F.: Ueber den Kreatingehalt des menschlichen Herzmuskels bei verschiedenen Krankheitszustanden, Biochem. Ztschr. **122**:152, 1921.

13. Vollmer, H.: Untersuchungen über den Kreatin- und Phosphorsäuregehalt verschiedener Herzteile, Ztschr. f. d. ges. exper. Med. **65**:522, 1929.

14. Cowan, D. W.: The Creatine Content of the Myocardium of Normal and Abnormal Human Hearts, Am. Heart J. **9**:378, 1934.

heart. Recently, Herrmann and his co-workers [15] found that the creatine content of the cardiac muscle varied from 85 to 132 mg., averaging 111 mg., in 13 patients who died of congestive heart failure; from 110 to 137 mg., averaging 123 mg., in 10 patients with chronic syphilitic aortic disease, and from 105 to 205 mg. in 32 patients with miscellaneous disorders. Hermann, Decherd and Oliver stated: "The results of our studies, and those of others, convince us that low human myocardial creatine values are more or less constant accompaniments of congestive failure and must be among the significant chemical changes that are associated with myocardial damage and insufficiency. Particularly significant are the extremely low total creatine contents of the myocardium from the infarcted areas in cases of coronary thrombosis." Their observations corroborate Cowan's finding of a low cardiac creatine content for patients with congestive heart failure.

Still more recently, and since our paper was completed and prepared for publication, Bodansky and Pilcher [16] have reported observations on 310 human hearts (212 males and 88 females). For the males the average creatine content of the muscle of the left ventricle was 157 mg. and for the females 163 mg. The general deductions which they have drawn from their data are in harmony with our interpretations, although their average findings are considerably lower than those reported by Cowan and by us. It appears that their averages were lower largely because of the fact that about 20 per cent of their figures were lower than any figures we encountered in the present and also in a later series. Bodansky's earlier findings [10] for the normal myocardium ranged from 220 to 285 mg.

Since dissociation of phosphocreatine results from slight injury to tissue incident to the most careful removal from the body and since its splitting is affected by p_H changes,[3] occlusion of the circulation, electric tetanization, fatigue and rapid decomposition occurring after death, determinations of the phosphocreatine content are impossible in human beings except in rare instances when biopsies or similar studies are made. For this reason estimations of the creatine content were made only for cardiac and voluntary muscle in this series.

15. Herrmann, G.; Decherd, G. M., and Schwab, E. H.: Some Biochemical Factors of Heart Failure, South. M. J. **29**:386, 1936. Herrmann, G.: A Possible Biochemical Basis of Myocardial Failure, in Medical Papers Dedicated to Henry A. Christian, Baltimore, Waverly Press, Inc., 1936, pp. 17-32; Insuficiencia cardíaca en términos bioquímicos, Arch. latino am. de cardiol. y hemat. **6**:49, 1936. Hermann, J.; Decherd, G., and Oliver, T.: Creatine Changes in Heart Muscle Under Various Clinical Conditions, Am. Heart J. **12**:689, 1936.

16. Bodansky, M.; Pilcher, J. F., and Duff, V. B.: Clinical Significance of the Creatine Reserve of the Human Heart, Arch. Int. Med. **59**:232 (Feb.) 1937.

Although voluntary [17] and cardiac muscles are distinctly different in structure and function, the voluntary muscle of normal persons has a relatively constant creatine content; the same is probably true of cardiac muscle. From this standpoint it is interesting to determine whether the ratio of creatine in these types of muscle remains constant in various disease conditions. Therefore, an attempt has been made in this paper (*a*) to compare variations in the creatine content of the heart with those of the pectoralis major muscle of patients dying of various diseases and (*b*) to interpret, if possible, some of the high and low creatine values found for cardiac and voluntary muscles.

EXPERIMENTAL METHOD

Estimation of Creatine in Muscle.—The method we employed for the estimation of the creatine content of muscle was described in a previous paper.[18] At the time it was stated to be a slight modification of the method of Rose, Helmer and Chanutin. Although that statement is true, the method as modified differs little from the one introduced by Folin in 1914. Folin pointed out at that time that it is possible with the aid of an autoclave to hydrolyze the creatine of a small sample of muscle without extraction. (The autoclave was first employed to convert creatine to creatinine by one of us [V. C. M.] in 1907). Rose, Helmer and Chanutin reduced the amount of muscle tissue used in the Folin method to about 1 Gm. and combined this with the Folin-Wu procedure for the estimation of creatine in blood. Since we had difficulty in securing perfectly clear filtrates from cardiac muscle when tungstic acid was used as a clarifying agent, we employed trinitrophenol for this purpose, as well as for the development of the Jaffé color reaction. In other words, the protein precipitable with trinitrophenol was filtered off before the development of color. The method used was, with this slight modification, the method of Folin, incorporating the refinements in technic introduced by Rose, Helmer and Chanutin.

STUDIES ON THE DOG

In a previous communication [18] we reported that the muscle of the left ventricle contains a higher creatine content than that of the right ventricle in the calf, the beef and the lamb as well as in human beings. The findings for 33 dog hearts bear out the same observation. The absolute creatine values for the left ventricle of the dogs ranged from 263 to 355 mg. per hundred grams of muscle, averaging 314 mg., and for the right ventricle the creatine concentration varied from 248 to 333 mg., averaging 291 mg. The data are presented in table 1, arranged according to cardiac weight. From an examination of the table it will be evident that there is no exact correlation with cardiac weight. However, if the average for dogs 1 to 10 is compared with the average for

17. Myers, V. C.: Creatine and Creatinine, Yale J. Biol. & Med. **4**:467, 1932.

18. Seecof, D. P.; Linegar, C. R., and Myers, V. C.: The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, Arch. Int. Med. **53**:574 (April) 1934.

dogs 24 to 33, it is found that the larger hearts had a creatine concentration that was about 5 per cent higher. It will be noted that like the ox,[18] the dog has about one-third higher concentration of creatine in the left ventricle than has the human being, namely, 314 mg., in comparison with 208 mg. (table 9). The percentage of difference in the creatine content of the respective ventricles was calculated by dividing the absolute difference in milligrams between the creatine contents of the two ventricles by the concentration in the muscle of the left ventricle.

TABLE 1.—*Creatine Content of Muscles of Left and Right Ventricles of Normal Dogs, Arranged According to Cardiac Weight*

Dog	Cardiac Weight, Gm.	Creatine Content, Mg. per 100 Gm. of Muscle		Difference Between Left and Right Ventricle	
		Left Ventricle	Right Ventricle	Mg.	%
1	225	328	305	23	7.0
2	185	308	274	34	11.0
3	160	331	295	36	10.9
4	155	327	311	16	4.9
5	140	294	284	10	3.4
6	127	317	307	10	3.2
7	120	346	326	20	5.8
8	115	321	297	24	7.5
9	114	334	306	28	8.4
10	114	328	302	26	7.9
11	113	344	320	24	7.0
12	113	303	295	8	2.6
13	112	303	290	13	4.3
14	110	277	256	21	7.6
15	106	309	293	16	5.2
16	99	341	318	23	6.7
17	98	355	290	65	18.3
18	95	309	276	33	10.7
19	95	284	272	12	4.2
20	90	275	258	17	6.2
21	89	348	333	15	4.3
22	85	318	258	60	18.9
23	84	319	307	12	3.8
24	82	306	291	15	4.9
25	80	293	265	28	9.6
26	75	340	308	32	9.4
27	71	263	248	15	5.7
28	71	301	285	16	5.3
29	70	319	281	38	11.9
30	69	326	299	27	8.3
31	67	297	285	12	4.3
32	65	322	307	15	4.7
33	57	315	263	52	16.5
Average		314	291	23	7.3

The differences ranged from 6 to 65 mg., or from 2.6 to 18.9 per cent with an average of 23 mg., or 7.3 per cent. The finding of a higher creatine concentration in the left ventricle supports our earlier observations on the hearts of man and of the ox, although it must be noted that the difference between the ventricles of the dog is much smaller. The average difference for 95 human hearts was 28.4 per cent and for 6 beef hearts 12.6 per cent, in comparison with 7.3 per cent for the dog. Compared with the human heart, this higher creatine concentration in the heart of the dog, together with the smaller difference between the ventricles, is obviously a fact of considerable significance from the

standpoint of comparative physiology, which will not be discussed further at this time.

Perfusion experiments on dog hearts in vivo showed that creatine can be removed from cardiac muscle. In these experiments a cannula pointing peripherally was inserted into the descending branch of the left coronary artery, the central end of the descending branch being ligated. The beating heart was then perfused through this cannula with aerated Locke's solution. By this procedure practically the only part perfused was the anterolateral and apical portion of the left ventricle. The remaining part of the left ventricle and practically the entire right ventricle received a normal blood supply through the circumflex branch of the left and right coronary arteries, respectively.

Area 1 in table 2 refers to the portion of the ventricle just peripheral to the point of introduction of the cannula, where the perfusion was greatest; area 2 refers to the apex of the left ventricle, where the

TABLE 2.—*Effect of Perfusion of Left Coronary Artery on Creatine Content of Cardiac Muscle in Dogs*

	Creatine Content, Mg. per 100 Gm. of Muscle						
	Left Ventricle						
Dog	Area 1	Area 2	Area 3	Right Ventricle	Cardiac Weight, Gm.	Volume of Perfusion Fluid, Liters	Comments on Perfusion
1	340	331	...	344	210	...	Unsuccessful
2	189	210	...	282	118	1.6	Successful
3	216	232	283*	304	155	3	Successful
4	180	325	...	326	125	3-4	Successful
5	183	...	340	311	125	2-3	Successful

* Area 3 was visibly perfused.

perfusion was less pronounced, and area 3 refers to the nonperfused or least perfused section on the posterior portion of the left ventricle. Consequently, as is shown in the table, creatine values were reduced more for area 1 than for other parts of the ventricle. The right ventricle was not perfused and was therefore used as a control, because the left ventricle was found to have a higher creatine content normally. In each case the perfusion was carried on until fibrillation began in the ventricles. This occurred in one instance in ten minutes (dog 1) and in another after as long as four hours (dog 5).

It is obvious that even a short perfusion of ten minutes' duration removed some creatine, because the values for the right ventricle were found to be higher than those for the left. There was a marked reduction in the creatine concentration of the perfused portion of the left ventricle in the experiments (dogs 2 to 5) which were continued for from one hundred to two hundred and forty minutes before fibrillation ensued. Perfusions of greater duration, viz., two hundred and forty minutes, and with greater volumes of perfusate did not remove more

creatine than those performed in the one hundred minute period, but this may have been due to better perfusion in the latter experiments or may have been incident to variable degrees of phosphocreatine dissociation.[19]

STUDIES ON HUMAN MATERIAL

All the human material was obtained immediately after death, and no discrimination was used in its selection. As a result, various types of conditions are included in this series, and only the 95 cases which were analyzed within twenty hours post mortem are included (with the exception of 1 case of lobar pneumonia [case 26], 1 each of acute and chronic infection, the cases of young patients and 4 cases of miscellaneous conditions, these being analyzed within thirty-six hours). In each case the creatine content of both ventricles of the heart and in most cases of the pectoralis major muscle was determined. The creatine concentration for both the cardiac and the voluntary muscle is expressed in milligrams per hundred grams of muscle.

In some of the cases to be presented many different clinical and pathologic diagnoses were made, so that it was difficult to segregate the cases into groups entirely on the basis of one uncomplicated condition. It was likewise difficult to separate such a miscellaneous lot of cases into groups in which the creatine content of either the cardiac or the voluntary muscle or both underwent certain definite changes, because of the lack of knowledge regarding all the functions and the origin of creatine and the reason for variations in the concentration of this constituent in the muscles. From the data on muscle creatine in the literature [4] it is apparent that (*a*) the creatine content of voluntary muscle may be reduced in muscular weakness, (*b*) it is primarily increased during fasting, after which it may decrease, (*c*) it is increased in other conditions associated with loss of weight (such as phosphorus poisoning and experimental scurvy) and (*d*) it tends to be lowered in chronic diseases, but may or may not be reduced in acute conditions (the value for cardiac creatine [20] is reduced in congestive heart failure).

Grouping the cases on a somewhat similar basis seemed to be a logical procedure to follow. Therefore, the following major groupings of the cases in which the diagnoses were definitely established appeared to give the most logical presentation of the data. The remainder of the cases which did not fall into one of these major classes were placed in a group of miscellaneous cases, mainly because each diagnosis was

19. Dr. C. J. Wiggers turned over to us these 5 hearts after the perfusion experiments noted.

20. Linegar, C. R., and Myers, V. C.: Further Studies on the Creatine Content of Heart Muscle, Proc. Soc. Exper. Biol. & Med. **32**:1016, 1935. Cowan.[14] Herrmann, Decherd and Schwab.[15]

complicated and the cause of death was questionable or could not be attributed primarily to one disease process or because the cases could not be placed in other groups.

Normal Values.—At present it does not appear that normal creatine values have been established for either the voluntary or the cardiac muscle of the human subject, although Bodansky [10] has reported analyses of various voluntary muscles of 3 subjects who died by accident. His figures for the pectoralis major muscle, as already stated, varied from 433 to 484 mg. per hundred grams of muscle. These figures are considerably higher than those hitherto reported, and until they are confirmed by additional figures it seems best to compare our figures for voluntary muscle with the average for the present data and other unpublished analyses, namely, about 400 mg. The average creatine content of cardiac muscle in this series was 208 mg. for the

TABLE 3.—*Creatine Content of Cardiac Muscle in Lobar Pneumonia*

Serial No.	Age, Yr.	Sex	Creatine Content			Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference, %		
45	75	M	263	150	43.0	475	472
24	29	M	247	181	26.7	400	427
111	47	M	233	173	25.8	350	397
43	61	M	227	130	42.7	300	483
26	22	M	216	130	39.8	275	428
Average			237	153	35.4	...	441

left ventricle and 149 mg. for the right. On the basis of these and other analyses, we have tentatively considered the normal content of creatine in the muscle of the left ventricle to be about 200 mg. and that in the right ventricle 150 mg.

Lobar Pneumonia.—The values for the creatine content of cardiac and voluntary muscles in lobar pneumonia are given in table 3. Although these values are close to those given by Bodansky [10] for 3 normal persons, it seems doubtful whether muscles of patients with lobar pneumonia can be considered normal, because of the fever and possible nitrogen retention. One patient (case 45) for whom the creatine content of the cardiac and voluntary muscles was in the higher range for this series showed no creatinine retention, and for the others determinations of the creatinine content of the blood were not made. The solid contents of the cardiac and voluntary muscles in cases 45, 111 and 43 were found to vary only slightly from the averages previously reported.[18] As will be noted, the creatine content of both the voluntary and the cardiac muscle was reasonably constant in these 5 cases of lobar pneumonia, but the values for the left ventricle and voluntary muscle were considerably above the average values.

In the group of patients with miscellaneous conditions, the data for which are given in table 9, are included 8 patients with bronchopneumonia and 3 with lobar pneumonia for whom pneumonia was not considered the major pathologic diagnosis. The creatine content of the muscle of the left ventricle of the patients with bronchopneumonia ranged from 219 to 259 mg., and averaged 238 mg., figures comparable with those for the patients with lobar pneumonia, given in table 3. The findings for the 3 patients with lobar pneumonia, however, were much lower than those given in table 3, namely from 145 to 188 mg., with an average of 174 mg. for the muscle of the left ventricle.

Cardiac Decompensation.—As may be observed in table 4, the creatine content of cardiac muscle is uniformly lowered in heart failure.

TABLE 4.—*Creatine Content of Cardiac and Pectoralis Major Muscle in Cardiac Decompensation*

Serial No.	Age, Yr.	Sex	Creatine Content			Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference, %		
103	33	M	220	144	34.5	250	433
35	26	F	194	146	25.0	375	346
97	50	M	192	178	7.3	750	348
50	46	F	187	125	33.2	300	387
15	62	M	183	120	34.4	750	...
116	47	M	178	111	37.6	560	348
17	77	M	163	127	22.1	375	...
86	76	M	162	153	5.6	400	497
65	58	M	160	124	22.6	450	...
60	60	F	146	109	25.3	825	...
38	43	M	138	114	17.4	275	367
Average			175	132	24.6	...	390

In all these cases the diagnosis was made clinically as being primarily cardiac decompensation, although the first case is one of acute circulatory collapse and secondary anemia following malaria treatment for tertiary syphilis and the creatine content of the muscle was similar to that in lobar pneumonia.

In 5 of the cases listed in table 4 the solid content was determined and found to be similar to that in cases of lobar pneumonia. This confirms the work of Cowan [14] and Calhoun and his co-workers,[21] who found that the water content of cardiac muscle of subjects dying of heart failure was not significantly altered, and eliminates variation in water content as a possible cause of the decreased creatine content. Cowan also stated that fibrous tissue contains less creatine than muscular tissue, but this factor was negligible in his series of cases. A study of variations in the fibrous tissue of the decompensated heart was not made in this series.

21. Calhoun, J. A.; Cullen, G. E.; Clarke, G., and Harrison, T. R.: Studies in Congestive Heart Failure: VI. The Effect of Overwork and Other Factors on the Potassium Content of Cardiac Muscle, J. Clin. Investigation **9**:393, 1930.

The creatine content of voluntary muscle was decreased slightly in all except cases 86 and 103, and the diminution bore no relation to the variations in cardiac muscle.

Diabetes.—For the 4 patients with diabetes, listed in table 5, the creatine content of the voluntary muscle was markedly reduced. In 2 of these cases the values for cardiac creatine were lowered as well, in

TABLE 5.—*Creatine Content of Cardiac and Pectoralis Major Muscle in Diabetes*

Serial No.	Age, Yr.	Sex	Creatine Content: Left Ventricle, Mg.	Creatine Content: Right Ventricle, Mg.	Creatine Content: Difference, %	Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.	Carbon Dioxide Capacity of Blood, Vol. %
99	67	F	275	152*	44.7	350	308	..
34	58	F	195	156	20.0	350	324	20 to 29
29	43	F	158	120	24.1	275	282	15
31	68	M	152	144†	5.3	500	339	..
Average			195	143	26.7	...	313	

* Slightly fatty.
† Greatly hypertrophied.

1 case there was slight diminution and in the remaining case the creatine value was even higher than the value in lobar pneumonia. Again there was a lack of correlation between the variations in the creatine content of cardiac and voluntary muscle. In cases 34 and 29 the carbon dioxide capacity of the blood was from 20 to 29 and 15 volumes per cent, respectively, indicating a markedly reduced alkali reserve.

TABLE 6.—*Creatine Content of Cardiac and Pectoralis Major Muscle in Carcinoma*

Serial No.	Age, Yr.	Sex	Creatine Content: Left Ventricle, Mg.	Creatine Content: Right Ventricle, Mg.	Creatine Content: Difference, %	Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.
94	45	M	255	179	29.8	300	...
68	52	M	192	167	13.0	300	347
51	58	M	174	135	22.4	250	...
32	23	M	170	120	29.4	275	310*
113	60	M	170	118	30.6	500	364
61	52	F	116	112	3.4	350	...
Average			180	129	35.3	...	340

* Osteosarcoma of right humerus. The right pectoralis major muscle showed 87 mg. of creatine; the left, 310 mg.

Carcinoma.—The cases listed in table 6 include those of carcinoma of the left lung, of the left cervical lymph nodes and of the esophagus, osteosarcoma of the right humerus, carcinoma of the tail of the pancreas and annular carcinoma of the transverse colon, listed in the order given in the table. In these cases there was a lowered creatine content of voluntary muscle, and, with the exception of the first case, there was always a lowered creatine concentration in the cardiac muscle.

Acute and Chronic Infections.—In comparison with the average creatine value, only 3 of the 15 patients with acute infection showed a lowered creatine content of cardiac muscle, namely 2 with septicemia and 1 with gangrene following prostatectomy; whereas 5 of the patients (encephalitis, encephalosis, meningitis, erysipelas and peritonitis) showed an elevated value for cardiac creatine. The rest of the patients showed a normal value for cardiac creatine. The creatine content of the voluntary muscle was lowered for 2 of 3 patients with septicemia, for 1 patient with peritonitis and for both patients with meningitis, i. e., in 5 of the 9 patients for whom estimations were made.

Half the 14 patients with chronic infection or tuberculosis had a lowered and 5 had an increased value for cardiac creatine, as compared with the average; whereas 5 of the 8 values for the creatine content of voluntary muscle were reduced.

TABLE 7.—*Creatine Content of Cardiac and Pectoralis Major Muscle in Uremia with Heart Failure*

Serial No.	Age, Yr.	Sex	Creatine Content			Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.	Blood Creatinine, Mg.	Carbon Dioxide Capacity of Blood, Vol. %
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference, %				
82	49	F	207	163	21.3	400	376	3.3	..
123	39	M	194	136	29.9	600	360	10.0	38
114	33	F	190	140	26.3	650	...	2.5	..
124	46	M	161	140	13.1	900	418	6.2	42-27
119	57	M	152	123	19.1	960	449	22.0	10
122	47	F	144	116	19.5	450	...	21.0*	6*
Average.....			176	136	22.3	...	401		

* Blood obtained post mortem.

Uremia and Uremia Plus Cardiac Decompensation.—When all the values for blood creatinine were placed in tabular form in descending order, it was found that neither the creatine content of voluntary nor that of cardiac muscle bore any relation to creatinine retention. However, by further analysis it was apparent that in most of the patients for whom the creatine content of the cardiac muscle was low, heart failure was a complication. On this account it seemed advantageous to rearrange the data on a different basis, with regard to uremia and uremia associated with heart failure.

In the patients with uremia plus heart failure (listed in table 7) the creatine content of the cardiac muscle bore no relation to the creatinine retention. The first patient had acute heart failure due to coronary thrombosis, with no reduction in the creatine content of the cardiac muscle, but the remainder of the values for cardiac creatine were low, like those for patients with cardiac decompensation (table 4). Two of 4 patients showed a low value for the creatine content of the voluntary

muscle. The last 2 patients showed a marked reduction in the carbon dioxide capacity of the blood.

On the other hand, the patients with uremia uncomplicated with heart failure (listed in table 8) tended to show a high value for creatine in both cardiac and voluntary muscle, although there did not appear to be any relation to creatinine retention or to the carbon dioxide capacity of the blood. Unfortunately, a determination of the creatinine content of the blood was not made in case 115, but the clinical and anatomic findings indicated severe uremia. There appeared to be no other explanation for the high creatine values in cases 18 and possibly 115 than that marked retention of creatine had a mass effect on the creatine-creatinine equilibrium.

Young Human Beings.—All the young human beings except the asphyxiated new-born infant died of acute infections. There is essentially no difference in the creatine content of the ventricular muscles

TABLE 8.—*Creatine Content of Cardiac and Pectoralis Major Muscle in Uremia*

Serial No.	Age, Yr.	Sex	Creatine Content			Cardiac Weight, Gm.	Creatine of Pectoralis Major Muscle, Mg.	Blood Creatinine, Mg.	Carbon Dioxide Capacity of Blood, Vol. %
			Left Ventricle, Mg.	Right Ventricle, Mg.	Difference, %				
18	60	M	369	283	23.3	500	520	25.1	38
115	60	F	348	158	54.6	450	564	....	..
105	54	M	254	209	17.7	300	437	5.4	..
120	47	M	249	204	18.1	525	...	17.8	21
121	53	M	216	196	13.9	500	485	5.8	47
Average.....			287	210	26.8	...	501		

of the new-born, and for all the other patients, ranging from 1 month to 4 years of age, the creatine content of the left ventricle was higher than that of the right. The value for cardiac creatine is low at birth and gradually increases to the value for adults within the first year. At the same time, the percentage of difference in the values for creatine in the two ventricles gradually increases, showing that the creatine content of the left ventricle increases more rapidly than that of the right and that the augmentation of the creatine concentration in the right ventricle is comparatively small. This fact may be correlated with the amount of work the two ventricles perform in the growing infant. For some unexplained reason, one patient, a child of 3 months who died of lobar pneumonia, pertussis and varicella, showed a creatine value for the left ventricle which corresponded to an extremely low value for the right ventricle. Furthermore, the weight of the heart of this infant was about twice that of others at this age period. With omission of this case, it is also apparent that creatine values similar to those for adults are reached in cardiac muscle at about 4 months of age, which is many months before saturation of the voluntary muscle

with creatine takes place. This is also shown by the observations of Vollmer,[18] but not by those of Beker [22] for other species.

Miscellaneous Conditions.—This group includes cases in which the primary cause of death was questionable or which did not fit into any other group. There were cases of leukemia, hepatic insufficiency, thyrotoxicosis, syphilis, intestinal obstruction, hemachromatosis and pellagra and cases in which the cause of death was not definite. The patient with leukemia showed a cardiac creatine content in the upper range for those with uremia and a voluntary creatine concentration definitely above the average normal value. Compared with the average, the patients with hepatic insufficiency showed an increased creatine content of voluntary and cardiac muscle, whereas 1 patient with cirrhosis and 1 with thyrotoxicosis showed a slightly lowered content in the

TABLE 9.—*Summary of Average Data on Creatine Content of Cardiac and Pectoralis Major Muscle*

		Creatine Content			Creatine of Pectoralis Major Muscle,	
	No. of Cases	Left Ventricle, Mg.	Right Ventricle, Mg.	Difference, %	Mg.	Grouping
	5	**287**	210	26.8	501	Uremia
	5	**237**	153	**35.4**	441	Lobar pneumonia
	15	223	151	32.3	393	Acute infections
	20	208	148	28.8	412	Miscellaneous
	9*	206	158	23.3	**328**	Young human beings
	14	206	158	28.2	382	Chronic infections
	4	195	143	26.7	**313**	Diabetes
	6	180	129	35.3	**340**	Carcinoma
	6	**176**	136	**22.3**	401	Uremia with heart failure
	11	**175**	132	**24.6**	390	Cardiac decompensation
Total and averages	95	208	149	28.4	395	

* Average age, 1 year.

cardiac muscle and an increased content in the voluntary muscle. Similarly, the patient with pellagra showed markedly decreased creatine values for cardiac and voluntary muscle, the 2 patients with syphilis showed a normal value for cardiac muscle and a lowered value for voluntary muscle and the patient with hemachromatosis and intestinal obstruction showed an increased cardiac concentration. The data for the rest of the patients are of little significance because of the questionable cause of death.

Summary of the Variations in the Creatine Values for Cardiac and Voluntary Muscle.—Table 9 presents a summary of the cases according to the adopted schemata, the data being arranged in the descending order of average creatine values for the left ventricle for each group. It shows that the lowest figures for adult voluntary muscle were

22. Beker, J. C.: Die Verteilung des Kreatins in Säugetierkörper, Ztschr. f. physiol. Chem. **87**:21, 1913.

obtained for patients with diabetes and carcinoma and the highest for those with uremia and lobar pneumonia. The patients with uremia and lobar pneumonia also showed the highest cardiac creatine concentrations encountered, while the lowest were shown by those with heart failure, regardless of whether or not this condition was associated with uremia.

It will be observed from an inspection of table 9 that, despite the fact that the lowest values for the creatine content of cardiac muscle were shown by patients with heart failure, these patients did not show the lowest values for the creatine content of voluntary muscle, the values being close to the average found for the series. Furthermore, the creatine content of cardiac muscle was not markedly lowered for those with diabetes, despite the fact that they showed the lowest values for the creatine content of voluntary muscle. It might be concluded

TABLE 10.—*Comparison of Creatine Content of the Pectoralis Major and Cardiac Muscle*

		Pectoralis Major Muscle		Ventricular Muscle		
	No. of Cases	Range, Mg.	Average, Mg.	Average for Left Ventricle, Mg.	Average for Right Ventricle, Mg.	Difference, %
	11	282-329	307	202	142	26.5
	11	330-363	347	208	160	23.1
	11	354-396	378	198	134	32.3
	11	397-426	410	195	145	32.3
	11	427-451	436	**232**	164	29.3
	12	452-564	484	**258**	163	**36.8**
Total and average	67		395			

from this that there is no relation between the level of the creatine concentration in voluntary and that in cardiac muscle. However, if the data are arranged on the basis of the concentration of creatine in the voluntary muscle, as in table 10, this does not appear to be entirely true. It will be observed that as long as the concentration of creatine in the voluntary muscle did not exceed about 425 mg., the concentration of creatine in the muscle of the left ventricle remained relatively constant, but when the concentration in the voluntary muscle exceeded this level, perhaps the normal saturation level, then there appeared to be a definite rise in the creatine concentration of the left ventricle. This is true of the last two groups of 11 and 12 cases, in which the average creatine content of the voluntary muscle was 436 and 484 mg., respectively. There was also some increase in the creatine concentration in the right ventricle, but the increase in the left ventricle was considerably larger, particularly in the last group of 12 cases.

COMMENT

It is highly improbable that one would find in any such indiscriminately chosen series of patients who died of acute and chronic infections, heart failure, uremia, diabetes, cancer and other disease conditions many who would show a normal concentration of muscle creatine. Strictly speaking, the cardiac and voluntary muscles cannot be considered normal except when the person is healthy and robust and meets death other than by way of disease.

Since there were no normal persons in this series and, furthermore, since there are insufficient data in the literature on which to define the normal values for the creatine content of voluntary and cardiac muscle, it appears that the only procedure to be followed at present is to take the average figures given in table 9 as the basis for comparison.

Although it is possible that the normal creatine content of human voluntary muscle is slightly in excess of the average given, namely, 395 mg., we doubt that the average normal content exceeds this figure by more than from 5 to 10 per cent. In a more recent unpublished study carried out in this laboratory on the same muscle (pectoralis major) Mangun obtained an average of 400 mg. for 34 persons. In another study in our laboratory Corsaro [23] obtained averages of 405, 402 and 388 mg., respectively, for the psoas major, rectus abdominis and sternocleidomastoid muscles in 74 cases. Thus it appears that the creatine concentration of human voluntary muscle obtained at autopsy is close to 400 mg. Since the number of figures both above and below this average in Corsaro's series about balanced each other, this figure may possess some importance. It is also significant, as will be noted in table 10, that as long as the creatine concentration of voluntary muscle does not exceed 425 mg., the average creatine concentration in the muscle of the left ventricle remains relatively constant, but when the creatine concentration of voluntary muscle exceeds this level there is also a rise in the creatine concentration of the cardiac muscle, suggesting that the normal saturation level of the voluntary muscle has perhaps been exceeded.

In the case of human cardiac muscle it is still more difficult to define the normal. However, one might assume that since the heart performs a less variable amount of work than voluntary muscle, its creatine concentration should remain relatively constant. In the present series of cases the creatine concentration of the cardiac muscle was found to be 208 mg. per hundred grams of tissue for the left ventricle and 149 mg. for the right ventricle. Partly on the basis of the distribution of the values, we are inclined to believe that our average figures are not far

23. Corsaro, J. F.: The Creatine Content of Human Voluntary Muscle, Proc. Soc. Exper. Biol. & Med. **35**:554, 1937.

from the normal creatine concentration. In a recent unpublished study Mangun obtained average creatine values of 199 mg. for the muscle of the left ventricle and 153 mg. for that of the right ventricle in 69 cases, the value for the left ventricle being about 4 per cent lower and that for the right ventricle about 3 per cent higher than in the present series. The average for both series is 204 mg. for the left ventricle and 151 mg. for the right ventricle, or, in round numbers, 200 mg. for the left and 150 mg. for the right ventricle.

In heart failure the creatine content of the muscles of both ventricles is uniformly lowered in cardiac decompensation except in acute conditions, such as coronary thrombosis. In some of these cases the creatine value seems to be lowered more for the left ventricle than for the right, as is shown by the small percentage of difference between the creatine values, which is suggestive of a tendency toward failure of the left side of the heart. We had hoped to find cases in which the creatine content of the muscle of the left ventricle would actually be lower than that of the right, to bear this contention out more definitely, but we were unable to do so. Conversely, any large percentage of difference in the creatine content of the two ventricles might be taken as an indication of failure of the right side of the heart. As a matter of fact, the figures in some of the cases suggest a tendency in this direction, but the data are not conclusive. Therefore, on the basis of the cases presented here, it appears that when the heart becomes decompensated it fails as a unit and not in a separate portion, such as in one ventricle, and that if the creatine content of one ventricle is lowered because of heart failure the creatine concentration of the other ventricle also falls. A more extensive series in which there was a larger percentage of difference and in which the left ventricle had a lower creatine content than the right might support the contention of the failure of the muscle of the left or right ventricle.

The fact that creatine can be washed out of cardiac muscle by perfusion indicates that part of it is present in a diffusible form. It has been shown that the diffusion of phosphoric acid [24] or creatine [25] is greater in fatigued than in resting muscle. This fact correlates with the greater dissociation of phosphocreatine under the same conditions.[3] Since the bound form of creatine is not diffusible, the source of the increased amounts of diffusible creatine must be the decomposition of phosphocreatine. It may be that the low creatine value for the fatigued heart (cardiac decompensation) is due to the greater breakdown of

24. Stella, G.: The Concentration and Diffusion of Inorganic Phosphate in Living Muscle, J. Physiol. **66**:19, 1928.

25. Tiegs, O. W.: Function of Creatine in Muscular Contraction, Australian J. Exper. Biol. & M. Sc. **2**:1, 1925. Eggleston, P.: The Diffusion of Creatine and Urea Through Muscle, J. Physiol. **70**:294, 1930.

phosphocreatine into a diffusible form or to inadequate resynthesis of phosphocreatine due to faulty nutrition of the heart and that the creatine thus released diffuses out of the muscle into the blood stream. (The recent work of Burns and Cruickshank [1b] is in harmony with this view.) Nevertheless, a low creatine content in cardiac muscle and heart failure are definitely related. It is now known that a low creatine value is associated with weakness of voluntary muscles, and it may be concluded that a low cardiac creatine content in heart failure and possibly in other conditions is connected in some way with the weakness of the cardiac muscle, but whether the lowering of creatine causes, contributes to or merely results from this condition remains to be determined.

Herrmann and his colleagues [15] suggested that in myocardial failure either suboxidation or anoxemia is present which causes an inadequate removal of lactic acid and that this product accumulates in the cardiac tissue. The lower p_H value results in increased hydrolysis of phosphocreatine and interferes with its resynthesis, and this may well hold its concentration at a low level and thus contribute to myocardial weakness.

In a study of variations in the potassium content in congestive heart failure Calhoun and his associates [21] concluded that cardiac fatigue and failure are due to loss of potassium from cardiac muscle and that this loss is the predisposing factor. It is well known that a certain balance of electrolytes, of which potassium, sodium and calcium are the most important cations, is necessary in living, functioning tissues. A marked disturbance of the osmotic equilibrium affects the physiologic functions of these tissues, as may be demonstrated, for example, by perfusion of the heart with potassium-excessive and potassium-deficient Ringer's solution. Consequently, potassium as well as the other cations cannot be overlooked in a chemical study of heart failure. Furthermore, it is probable that decreases of both potassium and creatine are associated in the failing heart, and since potassium,[26] creatine [18] and phosphorus [26a] show a higher content in the left ventricle than in the right, this fact indicates that creatine phosphoric acid probably exists as a potassium salt in cardiac muscle as well as in skeletal muscle. In a recent preliminary report Mangun and Myers [27] have noted that when the heart is hypertrophied there is a decrease in the concentration of creatine, potassium and phosphorus, generally somewhat in proportion to the ratios which exist in the dipotassium salt of phosphocreatine.

---

26. (*a*) Cullen, G. E.; Wilkins, W. E., and Harrison, T. R.: Electrolytes in Human Tissue: II. The Electrolyte Content of Hearts and Other Tissues from Cases with Various Diseases, J. Biol. Chem. **102**:415, 1933. (*b*) Calhoun and others.[21]

27. Mangun, G. H., and Myers, V. C.: Creatine, Potassium and Phosphorus Content of Cardiac and Voluntary Muscle, Proc. Soc. Exper. Biol. & Med. **35**:455, 1936.

It may be tentatively assumed that the low creatine values for voluntary muscle in diabetes and for cardiac muscle in heart failure are due to faulty nutrition, which results in incomplete resynthesis of phosphocreatine, with consequent diffusion of creatine from the muscles and creatinuria. The faulty nutrition in diabetes may be traced almost directly to the disturbed carbohydrate metabolism, and in heart failure this might be brought about by overwork or an inadequate blood supply. An explanation of the high creatine values encountered in uremia and pneumonia, on the other hand, is more difficult. It is generally recognized, as a result of experimental work on animals, that there may be a considerable increase in the creatine concentration of voluntary muscle in the early stages of starvation, while in the premortal stages there may be a marked drop in the muscle creatine. These changes are not due to fluctuations in the water content of the muscle, although the moisture content may have some influence on the creatine concentration. Normal muscle is able to take up and hold temporarily a small amount of creatine when this is administered. Since there is an equilibrium between creatine and creatinine, it is logical to expect that retention of creatinine as a result of renal disease might lead to an increase in the creatine concentration in voluntary and cardiac muscle. This is not invariably true, since in some cases of uremia with creatinine retention there is a low concentration of creatine in both voluntary and cardiac muscle. As already pointed out, it is a singular fact that in these cases heart failure has been manifest, whereas this has not been true in cases in which there was an increased creatine concentration in the cardiac muscle. Long before the discovery of phosphocreatine it was assumed that in some way the urinary creatinine coefficient (and with it the creatine content of muscle) is related to muscular efficiency. It may well be that factors which tend to maintain or raise the creatine content of cardiac muscle tend to retard the failure of ventricular muscle. Creatine and creatinine retention appear to offer the most plausible explanation of the high values encountered in some cases of uremia. Somewhat elevated values for the creatine of both voluntary and cardiac muscle have been encountered in lobar pneumonia and bronchopneumonia. The renal damage seems hardly sufficient here to explain the findings, but it is a well known fact that in cases of fever there is a marked increase in the excretion of creatinine (up to 35 per cent). A definite increase in the creatinine concentration of the blood has also been observed. It is possible that with the increased formation of creatinine in fever there is also an increased formation of creatine and that the renal excretion is unable to keep pace with this increased formation, thus leading to an increased concentration in the muscles. This seems to harmonize with the known facts. It is of interest to note that, in general, when elevation of the

creatine values is present there is a much greater increase in the creatine concentration in the muscle of the left than in that of the right ventricle.

In the foregoing discussion it has been shown that concentrations of creatine in cardiac muscle are increased or normal in lobar pneumonia and uremia and reduced in heart failure. The creatine content of cardiac muscle also is lowered in 50 per cent of the cases of tuberculosis, in 20 per cent of the cases of acute infection, in 83 per cent of the cases of carcinoma and in 75 per cent of the cases of diabetes. Likewise, the creatine value for voluntary muscle is increased or normal in cases of lobar pneumonia and uremia, whereas it is lowered in all cases of diabetes and carcinoma, in 5 of 10 cases of acute infection and in 5 of 8 cases of tuberculosis.

In 7 of 11 cases of cardiac decompensation the creatine concentration of the voluntary muscle is lowered, but not in direct relation to the decrease in the value for cardiac muscle. It is possible that the weakened condition of the heart permits less activity on the part of the patient and that disuse of the voluntary muscle results in atrophy and reduced efficiency. In cases of diabetes and such a condition as carcinoma the creatine value for voluntary muscle is consistently lowered, but the reduction in the creatine concentration in the cardiac muscle is comparatively small. Young human beings show a relatively higher creatine content of cardiac than of voluntary muscle, which indicates that the value for cardiac muscle reaches adult levels before that for voluntary muscle. In cases of uremia the creatine values for both cardiac and voluntary muscle tend to be high, and in cases of lobar pneumonia they are either somewhat elevated or about normal.

The bulk of the evidence obtained points to the concept that the variations in the creatine content of cardiac and voluntary muscle are not closely related. In other words, the circulatory and perambulatory systems of the body have individual functions to perform, although these functions are united in a coordinated organism. Although disease of one system has an influence on the other system, it is unlikely to exert more than a slight effect.

SUMMARY AND CONCLUSIONS

The cardiac muscle of the left ventricle of the dog has a higher creatine content than that of the right, which confirms the findings previously reported for other species. In comparison with man, however, the dog has a higher creatine concentration in the muscle of the heart, and the difference between the two ventricles is much smaller.

Perfusion of the heart of a dog in vivo with Locke's solution through the descending coronary artery markedly reduces the creatine content of the perfused area.

The creatine content of the heart of an infant is low at birth and progressively increases to adult values within a few months after birth.

The saturation level for the creatine of cardiac muscle is reached much earlier than that for the creatine of voluntary muscle.

In comparison with average values, the creatine content of the heart, i. e., of both the left and the right ventricle, is definitely lowered in cardiac decompensation. It is also usually slightly lowered in diabetes and carcinoma. On the other hand, the creatine content of the muscles of the left and right ventricles may be considerably increased in uremia uncomplicated with heart failure and in some cases of pneumonia.

Compared with average values, the creatine content of voluntary muscle (taking the pectoralis major muscle as an example) is reduced in diabetes and carcinoma and increased in uremia uncomplicated with heart failure and in the pneumonias.

The creatine content of cardiac and voluntary muscle may be reduced or increased in fairly constant ratios, but the major evidence points to the conclusion that variations in these two distinctly different muscles are not related, except in the cases in which the creatine content of both voluntary and cardiac muscle is elevated, probably as a result of nitrogen retention.

EFFECT OF JAUNDICE ON CHRONIC INFECTIOUS (ATROPHIC) ARTHRITIS AND ON PRIMARY FIBROSITIS

FURTHER OBSERVATIONS; ATTEMPTS TO REPRODUCE THE PHENOMENON

PHILIP S. HENCH, M.D.
ROCHESTER, MINN.

On April 1, 1929, a patient came to the Mayo Clinic complaining of chronic infectious (atrophic, rheumatoid) arthritis of four years' duration. He stated that a week previously, no medicine having been taken, painless jaundice suddenly developed. He said that on March 25, the day after he noted the jaundice, the pain and swelling in his joints began to diminish. When the patient was examined at the clinic the joints were symptomless; this complete symptomatic remission lasted five months with respect to the feet and eight months with respect to the hands. The phenomenon so impressed the patient that when he returned to the clinic two years later (May 1931), with moderately active arthritis, he reminded me that the only time his joints ever had been entirely free from pain was during and just after the jaundice. In the meantime, three other patients who had come under my observation had experienced the same phenomenon.

In the next four years I found a total of fourteen patients with "rheumatic" complaints (nine with chronic infectious arthritis, three with primary fibrositis and two with sciatic pain) who had experienced marked and generally complete symptomatic remission with the appearance of jaundice. In all cases the jaundice was of the intrahepatic type; in twelve cases it was due to cinchophen or derivatives of cinchophen, but two patients who had taken no medicine had the "catarrhal type" of intrahepatic jaundice. This indicated that jaundice, not cinchophen, was responsible for the dramatic remissions which lasted for a number of weeks or months, occasionally longer, after which symptoms recurred in most cases.

From the Division of Medicine, the Mayo Clinic.

Read before the Fifth Conference on Rheumatic Diseases held by the American Rheumatism Association, Atlantic City, N. J., June 7, 1937.

When these observations [1] were first reported I was unable to find any previous references to this phenomenon except three casual statements. With regard to cinchophen toxicity, Parsons and Harding [2] had noted the case of a woman with "rheumatism" who, after taking "Renton's hydrocin tablets" (containing approximately 5 grains [0.3 Gm.] of cinchophen), had jaundice and died. The writers stated that though the tablets "made her dizzy, the rheumatism disappeared." In a later report on cinchophen toxicity [3] they stated: "A history of the taking of cinchophen followed by disappearance of pain associated with the onset of jaundice is usually obtained." In another paper on cinchophen toxicity Grigg and Jacobsen [4] noted the case of a woman with arthritis of many years' duration. Cinchophen caused the development of jaundice, and she died. Without other comment the statement was made: "It is worthy of note that after the appearance of the jaundice she had no subjective symptoms of arthritis." Since then another brief passing comment has been called to my attention: In his clinical lecture entitled "On a Form of Chronic Joint Disease in Children," Still [5] (1897) stated: "Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever, and catarrhal jaundice to be each followed by distinct improvement of the joint symptoms."

Since the publication of my first report, Sidel and Abrams [6] and Borman [7] have made confirmatory observations.

---

1. Hench, P. S.: Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis, and Sciatic Pain, Proc. Staff Meet., Mayo Clin. **8**:430-436 (July 12) 1933; Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, J. A. M. A. **101**:1265-1266 (Oct. 14) 1933; The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis, and Sciatic Pain, Ann. Int. Med. **7**:1278-1294 (April) 1934. These observations were reported at the Second Conference on Rheumatic Diseases held by the American Association for the Study and Control of Rheumatic Disease, June 2, 1933.

2. Parsons, Lawrence, and Harding, W. G., Jr.: Fatal Cinchophen Poisoning: Report of Six Cases, Ann. Int. Med. **6**:514-517 (Oct.) 1932.

3. Parsons, Lawrence, and Harding, W. G., Jr.: Cinchophen Administration: Jaundice as an Untoward Effect, California & West. Med. **37**:30-32 (July) 1932.

4. Grigg, W. K., and Jacobsen, V. C.: Subacute Yellow Atrophy of the Liver Following Ingestion of Cinchophen and Allied Compounds, Ann. Int. Med. **6**:1280-1288 (April) 1933.

5. Still, G. F.: On a Form of Chronic Joint Disease in Children, Tr. Roy. Med.-Chir. Soc. **80**:52, 1897. Dr. Reginald Fitz called my attention to this reference.

6. Sidel, Nathan, and Abrams, M. I.: Jaundice in Arthritis: Its Analgesic Action, New England J. Med. **210**:181-182 (Jan. 25) 1934.

7. Borman, M. C.: Jaundice in Arthritis, with Report of Two Cases, Wisconsin M. J. **35**:890-891 (Nov.) 1936.

MATERIAL FORMING THE BASIS OF THIS REPORT

The present report summarizes my further observations (table 1) on this phenomenon from studies made of thirty-one additional rheumatic patients who experienced similar dramatic remissions of symptoms coincident with various types of jaundice and, of equal importance, notes on four patients with chronic infectious (atrophic) arthritis and nine patients with miscellaneous articular or neuritic conditions (other

TABLE 1.—*Effect of Jaundice on Thirty-One Patients with Rheumatic Disease*

		Jaundice			Remission				Subsequent Course				
					Duration, Weeks		Degree of Relief						
Disease	Average Duration, Years	Type	No. of Cases	Average Duration, Weeks	Average	Range	Complete	Almost Complete	As Before	Mild Recurrence	No Recurrence	Unknown	Died
Chronic infectious arthritis	5.5	Intrahepatic (cinchophen)	8	4.5	13.5	5- 43							
		Intrahepatic (other)	9	11.5	17.5	5- 39	12	7	10	8	..	1	..
		Obstructive (stone)	2	13.5	45.0	7- 82	63%	37%					
Total			19	9.0*	18.5*								
Primary fibrositis	5.2	Intrahepatic (cinchophen)	6	4.8	18.0†	4- 43†							
		Obstructive (stone)	2	3.0	54.0	5-104	9	..	3	4	1	..	1
		Obstructive (cancer of ampulla of Vater)	1	14.0	44.0	‡	100%						
Total			9	5.6*									
Miscellaneous: Lumbosacral and sciatic pain (2); hypertrophic arthritis of hips (Otto pelvis) (1)	2.3	Intrahepatic	3	5.0	5.0	.....	1 33%	2 67%	2	1	..	..	..

* General average.
† If one patient's remission of three years is included, the average is thirty-nine weeks.
‡ Until death occurred.

than atrophic arthritis or primary fibrositis) who were *not* relieved by jaundice. Space does not permit inclusion of detailed protocols of all the cases in which sudden remission was noted. Details concerning one of these cases were presented elsewhere;[8] data on representative cases are given herein.

Patients with Chronic Infectious (Atrophic) Arthritis Which Was Relieved by Jaundice.—Representative Case: A housewife aged 55

8. Hench, P. S.: A Clinic on Some Diseases of Joints: IV. The Inactivating Effect of Jaundice in Chronic Infectious (Atrophic) Arthritis and Fibrositis, M. Clin. North America **19**:573-583 (Sept.) 1935.

years had suffered for twelve years with severe chronic infectious polyarthritis which involved the shoulders, elbows, wrists, hands, hips and ankles. She had had much pain, stiffness and disability. Articular swelling usually was moderate, but at times her "fingers were so swollen that they stuck right out," and she could hardly wear shoes because of the swelling. Walking was much restricted, and she needed help to do her housework.

In April 1933 she was bedridden for six weeks because of articular disability. In July she began to take "Cahill's pills" (containing cinchophen) and continued to take them intermittently for ten weeks. On September 16 she noted that she was jaundiced and that the urine was dark. Three days later (September 19) the articular pains began to fade, and on the fourth day of the jaundice (September 20) she noted "complete relief" from pain, stiffness, redness and swelling. She

Fig. 1.—The knees and hands of a woman aged 55 who had had chronic infectious (atrophic) arthritis for twelve years. She obtained complete symptomatic relief from pain, stiffness, redness and swelling during cinchophen jaundice. These photographs were taken three weeks after the disappearance of jaundice and two weeks after the return of the activity of the arthritis. One may note thickening of the phalangeal joints and swelling of the wrists and knees.

stated, "I was able to do all my housework and felt real well except for a poor appetite." A month later (October 20) the jaundice began to fade, but articular pains had not returned. On October 24 the patient first noted a return of slight pain and swelling in one hand. She then came to the Mayo Clinic.

On October 27 (at the clinic) she was icteric (grade 2 + on a scale with 4 indicating the most extreme condition). The concentration of serum bilirubin was 10.3 mg. per hundred cubic centimeters; the van den Bergh reaction was direct. The knees and fingers were by then slightly swollen (fig. 1), but she said she "still had 90 per cent of the relief which jaundice brought to the joints." Ten days later, at the time

of her dismissal (November 6), the value for serum bilirubin had fallen to 4.8 mg. (direct reaction), and the joints were becoming worse, although she still had "only one-third as much trouble as before the jaundice." In June 1934 (when she last wrote me) her knees were considerably affected, but other joints that had been painfully involved prior to the jaundice were still unaffected, nine months after the onset of the remission. She was moderately obese, which may have been a factor in the early return of pain to the knees.

Synopsis of the Effect of Jaundice on Nineteen Patients with Chronic Infectious Arthritis: The effect of jaundice was noted by a total of nineteen patients who had chronic infectious arthritis, including the patient whose case has just been reported (table 1); the average duration of the disease was five and one-half years (range, one month to eighteen years). In eight of the nineteen cases of arthritis, intrahepatic jaundice due to cinchophen developed; the jaundice lasted for an average of four and one-half weeks (range, two to eight weeks). The remissions of symptoms lasted for an average of thirteen and one-half weeks (range, five to forty-three weeks).

In nine of the nineteen cases of arthritis, intrahepatic jaundice of different types developed: In six cases it was classified as catarrhal or epidemic infectious jaundice, and in the three other cases it was classified as due, respectively, to hepatitis and cholecystitis without stones, to hepatitis and portal cirrhosis with ascites and to syphilitic hepatitis (or possibly arsphenamine jaundice). The average duration of the intrahepatic jaundice in these nine cases was eleven and one-half weeks (range, ten days to six months). The remissions induced thereby varied in length from five to thirty-nine weeks (average, seventeen and one-half weeks).

In the remaining two of these nineteen cases of arthritis, obstructive jaundice developed, being due to gallstones. The average duration of the jaundice was thirteen and one-half weeks and that of the remissions was forty-five weeks. The unusual average length of the jaundice and the remissions in these two cases resulted from the fact that one patient had a stone in the common bile duct which caused jaundice of varying intensity for about twenty-four weeks and a complete remission of symptoms for nineteen months (eighty-two weeks). In the other case, jaundice of three weeks' duration produced a complete remission of articular symptoms for seven weeks.

Two of these nineteen arthritic patients experienced jaundice more than once; the result of each attack of jaundice has been included in these averages and will be discussed later.

In summary, the nineteen patients who had chronic infectious arthritis had jaundice which lasted on an average nine weeks and a

remission of articular symptoms which lasted on an average twice as long (eighteen and one-half weeks). Twelve (63 per cent) of the patients received complete relief from their active articular symptoms; and seven (37 per cent) of the patients had almost complete relief; for example, they had no pain while at rest and no swelling or tenderness but had slight aching after weight-bearing, or they had no stiffness or pain while at rest or on motion but had slight articular tenderness. Relief from stiffness, of course, means relief from the articular or muscular stiffness due to active inflammation and spasm of muscles and joints and not that due to residual structural damage.

Patients with Primary Fibrositis Which Was Relieved by Jaundice.—Periarticular and extra-articular (as well as intra-articular) fibrous tissues are involved in practically all cases of chronic infectious arthritis; thus, associated or secondary fibrositis is a part of this disease. In the following cases of primary fibrositis, however, there was no evidence of arthritis or of intra-articular disease. Primary fibrositis is characterized by chronic stiffness, aching and soreness of muscles (intramuscular fibrositis) or of joints (periarticular fibrositis) or of both. The condition presents no evidence of intra-articular disease, such as hydrops, significant swelling, roentgenographic alterations or deformity from intra-articular disintegration, nor does it give evidence of the systemic, clinical and chemical manifestations which make up the syndrome of chronic infectious arthritis, such as loss of weight, hypochromic anemia, increase in the sedimentation rate and increase in the nonfilamented cell count. Periarticular fibrositis is often erroneously diagnosed as mild arthritis. The criteria employed at the clinic for the diagnosis of primary fibrositis have been published.[9]

Representative Case: On Feb. 15, 1935, a physician aged 64 suddenly acquired afebrile stiffness and soreness of the knees, elbows and shoulders, without redness or swelling. The disability progressed, rapidly, so that by February 18 he had to use a cane in walking. During the next week the degree of stiffness and soreness increased markedly, so that he was unable to walk, comb his hair, write or clothe himself. He had great difficulty in feeding himself, and because of soreness, stiffness and weakness of the joints of the arms and hands he dropped a coffee cup on several occasions. On March 5 he gave up his practice and went to a spa. He was practically helpless; he could not feed or dress himself and required the services of a nurse night and day. He was taken in a wheelchair for immersion baths and was lifted by attendants into the water. Only a few hours of relief was afforded by

9. Slocumb, C. H.: Differential Diagnosis of Periarticular Fibrositis and Arthritis, J. Lab. & Clin. Med. **22**:56-63 (Oct.) 1936. Hench, P. S.: Acute and Chronic Arthritis, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1935, vol. 3, chap. 1, pp. 104-175.

the baths; to augment this relief, cinchopyrine (cinchophen, aminopyrine, calcium carbonate and colchicine) was given daily.

Prior to March 10 the patient had severe pains and disability. On March 10 he thought his eyes were slightly yellow. On March 11 he noted frank jaundice, and on that day he said that his pains began to fade. This physician described the experience further as follows: "The next day (March 12) all articular symptoms were gone. I could walk freely to the bath. I thought the baths and medicine had cured me, so I dismissed both my nurses. By afternoon I felt so well that it seemed foolish to stay longer, so I walked downtown (a small town) for my railroad tickets; but that evening, on the advice of my physician, I decided to stay because of the jaundice and some nausea." During the next few days the patient walked freely about his hotel and to the baths and had no symptoms of rheumatism. On March 16 he went home, but because the jaundice persisted, he came to the Mayo Clinic on April 1.

The jaundice was then fading; the concentration of serum bilirubin was 3.4 mg. (direct reaction). All the joints were entirely painless on voluntary and even on forced motion. There was no articular tenderness or aching or periarticular thickening. Jaundice lasted five weeks. The patient remained completely free from rheumatic disability for ten months. On Jan. 15, 1936, he first noted a return of mild pains in the joints, which have persisted (mildly) to the time of writing.

Synopsis of the Effect of Jaundice on Nine Patients with Fibrositis: Nine patients who had primary fibrositis, including the one whose case has just been reported, experienced complete symptomatic remissions coincident with jaundice (table 1). All had periarticular fibrositis, and three had intramuscular fibrositis also. The duration of the disease averaged five and one-fifth years. In six of these nine cases of fibrositis, intrahepatic jaundice was caused by cinchophen and lasted from three to ten weeks, with an average of four and four-fifth weeks. Excluding one case, the complete remissions of fibrositis lasted for an average of about eighteen weeks (range, four to forty-three weeks). One patient had no recurrence of symptoms for three years; when this patient is included, the average length of the remissions is raised from eighteen to thirty-nine weeks.

In three of the nine cases of fibrositis, obstructive jaundice developed, in two cases as a result of stones and in one case as a result of carcinoma of the ampulla of Vater. Jaundice from cholelithiasis lasted for an average of three weeks (range, one to five weeks), but the average length of the symptomatic remissions was fifty-four weeks, because one of these two patients, who had obstructive jaundice twice, had complete remission of fibrositis for two years after one of the attacks of cholelithiasis with jaundice. Otherwise the remissions lasted five weeks in the one case and five months after the second attack of

jaundice in the other case. In the case in which obstructive jaundice developed as a result of cancer of the ampulla of Vater, the jaundice lasted fourteen weeks prior to surgical relief of the biliary obstruction. The patient had had stiffness and soreness of many joints practically constantly for twenty years. At the clinic she stated that until the jaundice had begun she had not had any real relief of the articular symptoms in all the twenty years. Thereafter, until her death on July 19, 1934, the joints were free from symptoms, a remission of forty-four weeks.

In summary, in the nine cases of fibrositis, jaundice developed, with an average duration of five and three-fifth weeks. In every instance the symptomatic remission induced thereby was complete, and the patient was entirely free from symptoms of stiffness, soreness, tenderness or aching. This contrasts with the fact that only 63 per cent of the arthritic patients obtained complete relief, since the remaining 37 per cent had almost complete relief. One would expect a more complete effect in fibrositis, wherein pathologic changes are so much less pronounced than in chronic infectious arthritis.

Additional Patients Whose Articular Symptoms Were Relieved by Jaundice.—With the onset of jaundice, two patients who had chronic lumbosacral and sciatic pains and one who had an Otto pelvis and hypertrophic arthritis of the hips were relieved of symptoms. The duration of their pains prior to jaundice averaged two and three-tenths years.

1. A man aged 44 years had severe pain in the lumbosacral and sciatic region after influenza in February 1934. He was in bed two weeks, and thereafter he could not work for three months. Less severe but annoying pains continued until March 1935, when the pain in the back became worse after he changed an automobile tire. He took 182 capsules of oxyliodide (cinchophen hydriodide) during the next few weeks and on April 1 noted slight jaundice, dark urine and light stools. He observed that on that day his back was definitely better. Either on April 3 or 7 he said to a relative, "My backache is gone completely. It seems strange to me that my back has stopped hurting since my jaundice came out. I wonder if there is any connection between the two."

The patient was seen at the clinic about three weeks later (May 29), still deeply jaundiced (serum bilirubin content, 21.4 mg., direct reaction). He stated that prior to the development of jaundice, he had had considerable difficulty sliding on and off a high bank clerk's stool and changing his position in bed. At the clinic he had full, free motion of the spinal column and extremities and no pain. I could not elicit any tenderness or pain even by pounding with my fist over the previously affected regions or by subjecting his joints to strenuous passive motion. Roentgenograms gave evidence of slight narrowing of the lumbosacral joint and hypertrophic changes of the right lumbosacral facet and of the right fourth and fifth lumbar facets. It was reported that neurotropic streptococci were recoverable from the nasopharynx and that there was no evidence of an increase in antistreptococcic immune bodies in the presence of jaundice; the significance thereof will be discussed later.

The value for serum bilirubin rose to 28.6 mg. and then fell to 6 mg. at the time of the patient's dismissal, May 23. A month later the jaundice (of eleven

weeks' duration) had ended. The analgesia lasted at least that long. The patient did not recall just when his pains began to recur, but for the two years prior to May 1937 his back had been "much less painful than it used to be before the jaundice."

2. Another patient whose lumbosacral and sciatic pain was relieved by jaundice was a man aged 49 who had fever and severe pain in the small of the back, right hip and thigh late in April 1934. The condition had been diagnosed as due to influenza and sciatica. In June, after being in bed for six weeks with severe pain, he began to use crutches, and in the middle of July he took six bottles of a patent remedy for rheumatism because of chronic backache. On October 8 he became jaundiced. The next day he had fever and epigastric distress, but, he said, "On waking I noticed I had no rheumatism, and my back felt fine." For about a week he had no pain; then slight pain ("20 per cent as much as before") returned. Jaundice lasted a short time, starting to fade about October 11, when he came to the clinic.

The value for serum bilirubin was 4.4 mg. (direct reaction). The spinal column was stiff, and there was some tenderness in the right iliac and gluteal regions. His pains, however, were much less severe than formerly. On October 19, when the value for serum bilirubin had fallen to 1.6 mg. (direct reaction), his backache became as severe as before the occurrence of jaundice. The diagnosis was spondylitis, cirrhosis of the liver, with jaundice, and splenomegaly. There was some discussion as to how much (if any) of the symptomatology might be due to undulant fever. The serum agglutinated Brucella abortus in a dilution of 1 to 160; he had lost sixteen calves because of disease due to that organism in March.

Moderate jaundice of short duration apparently had relieved the patient's backache and sciatic pain completely for a few days and partially for a few days more. In January 1935 he had no pain except in the neck.

3. A man aged 49 had had pain in the left hip and thigh for six years. Jaundice, presumably of the spontaneous catarrhal type, appeared; his local physician noted an icterus index of 20 (roughly analogous to a value for serum bilirubin of about 3 mg.). Jaundice lasted about three weeks; part of this time he was completely relieved; the rest of the three weeks he was notably, but incompletely, relieved of pain. At the clinic, roentgenograms revealed marked hypertrophic arthritis of both hips, with protrusion of the femoral head into the acetabulum. The condition was thought to be not ordinary chronic infectious (atrophic) arthritis or simple senescent (hypertrophic) arthritis but hypertrophic arthritis associated with an Otto pelvis. The patient came to the clinic on May 23, 1934, a week after the jaundice had left; pain was then returning in the usual situations. The value for serum bilirubin was only 1.4 mg. (direct reaction).

The conditions presented by these three patients were admittedly not as clearcut and the effects of coincident jaundice were not as dramatic as those of the patients with arthritis and fibrositis, but the reports are included in order that it may be considered to what degree the analgesic or inactivating effect of jaundice may or may not be relatively specific for diseases more obviously rheumatic.

Patients with Arthritis or Fibrositis Who Had Repeated Jaundice.—Two of the patients who had arthritis and two of those who had fibrositis had jaundice more than once (table 2).

A woman aged 49, who had had chronic infectious arthritis (fig. 2) uninterruptedly for fifteen years had marked spontaneous painless jaundice which lasted twenty-five weeks. A complete symptomatic remission developed and lasted nine months; then the symptoms returned as before. Four years later, "slight" jaundice developed after she had taken only 4 tablets of cinchophen. The jaundice lasted three weeks, and the patient had no relief from the arthritis therewith. The following year, without further medication, "very mild" (spontaneous) jaundice developed, lasted two weeks and produced no symptomatic remission.

This indicates, again, as noted in my first report, that mild jaundice will not produce the phenomenon; a certain intensity of jaundice is necessary to invoke it.

TABLE 2.—*Effect of Repeated Jaundice on Four Patients with Arthritis or Fibrositis* *

Diagnosis	Duration, of Disease, Years	Jaundice			Remissions		
		Type	Degree	Length, Weeks	Degree	Length, Months	Subsequent Course
Chronic infectious arthritis	15	1. Spontaneous painless	Marked	25	Complete	9	As before
	19	2. Cinchophen ? (4 pills)	Slight	3	None		
	20	3. "Spontaneous"	Very mild	2	None		
Periarticular fibrositis	1/12	1. Obstructive (stone)	Moderate	1	Complete	24	Pains returned
	2½	2. Obstructive	Marked	3	Complete	5+	No pain to date
Diffuse fibrositis and chronic hypertrophic arthritis (traumatic and senescent)	14	1. Cinchophen ?	?	4-5	Complete	8	As before
	15	2. Cinchophen	Serum bilirubin value of 12.7 mg.	6	Complete	4¼	As before
Chronic infectious arthritis	9	1. Cholecystitis; hepatitis	?	6	Partial	?	
	11	2. Cholecystitis; hepatitis	Moderate	1	Complete	¾	As before

* Symptomatic remissions were produced when marked or moderate jaundice was present; mild jaundice had no effect on the rheumatic symptoms.

Three other patients, however, received marked or complete amelioration of articular symptoms on two occasions each (table 2). In each instance the jaundice was moderately severe or marked. Insufficient data are at hand to make it possible to state whether subsequent periods of jaundice are more or less effective in producing prolonged analgesia than is an initial attack of jaundice.

Patients Whose Articular Disease Was Not Affected by Jaundice.—At the time of my first report [1] I had not seen a patient with jaundice who had not received more or less complete, although temporary, relief from preexisting rheumatic pain. However, records of the clinic contained data on three patients, two with chronic infectious arthritis, one

with sacro-iliac pain and one with sciatic pain, which indicated that jaundice was not always associated with relief from pain; these cases were discussed in the first report as cases 13 to 15.

Observations have been made on thirteen additional patients who were unrelieved by jaundice (table 3). In the presence of mild jaundice, four patients with chronic infectious arthritis were unrelieved of arthritic symptoms. Three patients who had gout suffered from two or more painful attacks of gouty arthritis in the presence of jaundice which, although mild in two cases, was fairly intense in one case. In one patient jaundice of uncertain intensity developed during the "silent or prodromal phase" of rheumatic fever; the jaundice did not cause the subsequent attack of rheumatic polyarthritis to be aborted. In the presence of fairly intense jaundice, there was marked articular pain in

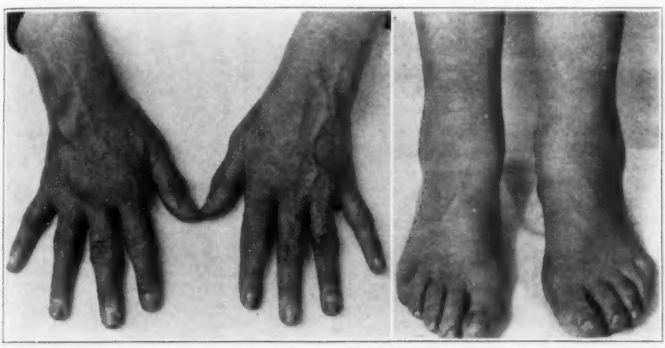


Fig. 2.—The feet and hands of a woman aged 49 who had had chronic infectious arthritis for fifteen years. She obtained complete symptomatic relief which lasted for nine months; it began with the onset of a spontaneous painless but marked jaundice of twenty-five weeks' duration. Two subsequent short attacks of mild jaundice produced no relief of the articular symptoms. These photographs were taken after the end of the symptomatic relief. One may note swelling of the right wrist, of certain midphalangeal joints and of the ankles.

a case of a juxta-articular malignant growth and in two cases of "toxic or infectious arthralgia," and marked neuritic pain was present in a case of postherpetic neuralgia and in a case of ischemic neuritis.

In some of these cases, particularly those of chronic infectious arthritis, the symptoms may not have been ameliorated because the jaundice was slight, below the "zone of therapeutic effectiveness." In other cases, however, the jaundice was of an intensity which is effective in chronic infectious arthritis, yet articular symptoms were not relieved. These observations suggest, therefore, (1) that the phenomenon is quantitative, dependent on a certain intensity of jaundice, and (2) that

it may be relatively specific for infectious (atrophic) arthritis and for primary fibrositis. Further studies of cases in which relief is *not* produced by jaundice may yield data on the mechanism and specificity of the reaction in the cases in which relief is obtained.

TABLE 3.—*Observations on Thirteen Patients Whose Articular or Neuritic Symptoms Were Not Relieved by Jaundice* *

Painful Condition Apparently Unrelieved by Jaundice	Jaundice		
	Type	Duration	Intensity
1. Chronic infectious arthritis, 4 yr.	Obstructive jaundice	3 wk.	Mild; "eyes a bit yellow"
2. Chronic infectious arthritis, 2 yr.	Cinchophen	8 wk. (?)	Uncertain; mild (?); never in bed; no relief during 2 pregnancies
3. Chronic infectious arthritis, 9 yr.	Jaundice with agranulocytosis (aminopyrine ?)	4 days	Mild; maximum serum bilirubin value, 3.2 mg.; direct van den Bergh reaction
4. Chronic infectious arthritis (?), 8 yr.; creaky painful joints; neuromuscular pains	Hemolytic	.....	Serum bilirubin value, 3.8 mg.; indirect van den Bergh reaction
5. Gouty arthritis, 2 attacks	Obstructive jaundice and cancer of pancreas	2 mo.	Serum bilirubin value, 14.5 mg. during one short painful attack
6. Gouty arthritis, several attacks	Hemolytic	.....	Uncertain; acute gout after splenectomy when serum bilirubin value was 1.3 mg.; direct van den Bergh reaction
7. Gouty arthritis, several attacks	Hemolytic	.....	Fluctuating; serum bilirubin value, 6.3 mg.; direct van den Bergh reaction during 1 attack
8. Acute rheumatic fever, third attack	Catarrhal jaundice; 4 days later, onset of rheumatic fever	1 wk.	Uncertain
9. Sternoclavicular swelling, acutely painful; metastasis (?); specific infection ?	Obstructive jaundice; cancer of pancreas	.....	Serum bilirubin value, 11.3 mg.; falling
10. Arthralgia, recurrent, febrile	Jaundice from hepatitis; cirrhosis	6 yr.	Uncertain; at one time serum bilirubin value, 7 mg.; direct van den Bergh reaction
11. Arthralgia; painful tender joints; hydrops in one	"Infectious"	Several mo.	Serum bilirubin value falling; 6.4 to 2 mg.; direct van den Bergh reaction
12. Neuralgia, postherpetic	Obstructive, recurrent (cholecystitis; stone in common duct); 3 or 4 attacks of jaundice since onset of neuralgia	.....	Uncertain; "pretty yellow each time"
13. Neuritis (ischemic) after gynergen	Partial stricture of common duct	.....	Serum bilirubin value, 11 mg.; falling

* Four patients had chronic infectious (atrophic) arthritis, and nine had articular or neuritic symptoms from conditions other than chronic infectious arthritis or fibrositis. The observations suggest that the phenomenon is relatively specific for chronic infectious arthritis and for primary fibrositis, but, even so, it bears a quantitative relation to the intensity of the jaundice.

In connection with the beneficial effect which jaundice seems to have on certain rheumatic diseases and in view of cases 10 and 11 (table 3), particularly the former, wherein arthralgia seemed to be a symptom coincident with febrile attacks of deepening jaundice, it is of interest

to note that Freund [10] has briefly described "arthritis posticterica;" Glénard and Françon [11] have discussed *rheumatismes chronique d'origine hépato-biliare,* and recent French monographs [12] on diseases of joints include paragraphs on *le rheumatisme chronique biliare* (enlargement of the ends of the bones, synovitis and pains in the joints—a form of osteo-arthropathy rather than a type of arthritis), described by Gilbert and Fournier (1895),[13] by Gilbert and Lereboullet (1902) [14] and by Wynn (1904).[15] This entity has not been described in the United States, so far as I am aware, and I am not sufficiently familiar with it to know whether it should be regarded as established. Taylor [16] (1895) described the case of a young man who had "multilobular and unilobular hepatic cirrhosis" from the age of 6 years and who died of pyemia at the age of 20. During the last week of his life and while he was jaundiced (degree unstated), acute polyarthritis developed. His condition probably was pyemic arthritis; however, it was not "biliary rheumatism." Rolleston and McNee [17] (1929) stated that toxic and pyemic arthritis may occur in cases of single or "tropical liver abscess," such as that caused by Endamoeba histolytica. They said they regarded biliary rheumatism skeptically. In his recent monograph Weiss [18] (1935), however, mentioned stiffness of the articulations, especially of the hands and of the nape of the neck, as one of the minor diagnostic signs of latent hepatic insufficiency. In whatever manner my own two cases should be labeled, obviously the arthralgia and the soreness of fibrous tissue were not due to primary fibrositis or to ordinary chronic infectious arthritis.

---

10. Freund, Ernst: Gelenkerkrankungen: Einführing in die Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1929, p. 139.

11. Weissenbach, R. J.; Glénard, R., and Françon, F.: Rheumatismes chronique d'origine hépato-biliaire, Nutrition **2**:117-138, 1932.

12. Marinesco, G.: Rheumatisme chronique par autointoxication, in Roger, G. E. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine et de thérapeutique, Paris, Masson & Cie, 1924, pp. 552-553. Mouriquand, Georges, and Michel, Paul: Rheumatisme chronique, in Weill, A.: Maladies de la nutrition, Paris, A. Maloine et fils, 1922, vol. 23, p. 612.

13. Gilbert, A., and Fournier, L.: La cirrhose hypertrophique avec ictère chez les enfants, Compt. rend. Soc. de biol. **47**:419-420, 1895.

14. Gilbert, A., and Lereboullet, P.: Le doigt hippocratique dans les cirrhoses biliaires, Gaz. hebd. de méd. **7**:1-4, 1902.

15. Wynn, W. H.: Secondary Hypertrophic Osteo-Arthropathy, Birmingham M. Rev. **55**:139-155, 212-228 and 282-302, 1904.

16. Taylor, Frederick: Cases of Cirrhosis of the Liver in Children, with Some Remarks on Cirrhosis [case 2], Guy's Hosp. Rep. **52**:53, 1895.

17. Rolleston, Humphrey, and McNee, J. W.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, London, The Macmillan Company, 1929.

18. Weiss, Samuel: Diseases of the Liver, Gallbladder, Ducts and Pancreas: Their Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1935, p. 282.

CHARACTERISTICS OF THE PHENOMENON; RECAPITULATION

Specificity.—On the basis of present information, then, the phenomenon seems relatively specific for chronic infectious arthritis and for primary fibrositis (including certain cases of sciatica). I have not had the opportunity to see the phenomenon in a case in which disability prior to jaundice was chiefly or solely due to senescent hypertrophic arthritis. However, four of the patients who received complete relief from articular and muscular symptoms when jaundice appeared had this form of arthritis coincidentally with the main disease: chronic infectious arthritis in two cases and chronic periarticular and intramuscular fibrositis in two cases. When each of the patients came to the clinic in the course of, or after, the attack of jaundice, roentgenographic or objective evidences of symptomless senescent arthritis were visible (spurs in the lumbar or cervical portions of the spinal column and Heberden's nodes), but the history indicated that the previous disability, which had been temporarily inactivated completely by jaundice, was mainly if not wholly due to rheumatism of another type—infectious arthritis or diffuse primary fibrositis. It could not be determined whether the patient had had symptomatic, if incidental, senescent arthritis, which also had been made asymptomatic, or whether the senescent arthritis had been asymptomatic before the development of jaundice.

Aside from the one inconclusive observation on rheumatic fever, I have not seen a patient who had this disease and coincident jaundice. As has been noted, gouty arthritis apparently may be acute and painful, in spite of fairly severe jaundice. At least two patients who had arthralgia of undetermined type, one patient with neuralgia and one with neuritis experienced pain in the presence of jaundice, not of marked intensity, however. Further observations may indicate that more intense degrees of jaundice than those thus far encountered in association with these diseases may be more effective, stressing the quantitative rather than the specific nature of the reaction.

Relative Effectiveness of Different Types of Jaundice.—The phenomenon apparently can be precipitated by almost any type of obstructive or hepatogenous jaundice provided it is intense enough. Most of the common types of jaundice are represented in the group of conditions in which relief was obtained. The effectiveness of these types of jaundice seems to be more quantitative than qualitative. The data in table 1 seem to suggest that obstructive jaundice due to stones produced longer remissions than intrahepatic jaundice. But this conclusion, based on a study of only four cases of obstructive jaundice, in two of which the jaundice was inordinately prolonged, should not be accepted as final. No instance of "successful" hemolytic jaundice is included, probably because in none of the three cases in which hemolytic jaundice occurred was the con-

centration of serum bilirubin particularly high; indeed it rarely ever is high in this type of jaundice. It remains to be noted whether the phenomenon may occur in the presence of severe hemolytic jaundice. To aid the search for the responsible agent in jaundice it is important to determine this point because of the chemical differences between hemolytic and other types of icterus.

Promptness of the Reaction.—Data on the time of appearance of the analgesia as it occurred in this second series of patients agree with those noted in my first series. The thirty-one patients of this series had thirty-four effective periods of jaundice, three having had more than one such period. In sixteen instances the patients were not sure of the exact time relation between the onset of recognized visible jaundice and the onset of relief of pain and were content with the statement that when the jaundice appeared (or with the onset of jaundice), the pain disappeared. In general, the onset of relief was noted promptly with the appearance of visible jaundice. Relief of pain was first noted on the first day of visible jaundice three times, on the second day four times and on the third day three times. Three patients who were disturbed by intestinal symptoms coincident with jaundice stated that toward the end of the first week they suddenly realized that the rheumatism was gone. It is likely that analgesia may have occurred sooner and may have been unrecognized owing to concern over the jaundice.

One of the patients in my first series (case 16) was rather insistent that the swelling and pain in the joints disappeared about six weeks before the onset of visible jaundice but with the onset of the early preicteric symptoms of toxic (cinchophen) hepatitis. So, too, four patients of this series stated that, according to their recollection, definite analgesia appeared several days before jaundice was noted. One patient noted it "when the urine began to be dark, one week before the jaundice was noticeable." Another, whose case will be described briefly hereafter, noted analgesia "one or two days before jaundice." One patient who experienced the phenomenon twice, dated the first period of analgesia as beginning one week before and the second period three to six days before the onset of jaundice. The fourth patient I examined in May 1934 because of severe spondylitis, which was still active after eighteen years. He was unable to work and could walk only three blocks with a cane. He returned to the clinic on December 17 with severe hepatitis, jaundice and ascites. His jaundice was first noted about September 1, but, he stated, "During the first week of August I began to get well awfully fast, and within two weeks my rheumatism was cured. My joints feel so well I think it will never return." He could walk at least three fourths of a mile (a kilometer) without a cane, and he said he felt better than he had for twenty years. The concentration of serum

bilirubin was 15.4 mg. (direct reaction). Roentgenograms revealed marked spondylitis of the infectious (atrophic, rhizomelic or ankylosing) type. Examination revealed no soreness or tenderness anywhere, merely residual, inactive, or symptomless, spondylitis. The patient was dismissed on December 28 and died on March 12, 1935, having had, according to his local physician, "very little active arthritis after the jaundice."

Too much credence cannot be given these statements suggesting an analgesic effect from subclinical jaundice, because patients differ greatly as to the keenness of their observations. A slight or even a definite visible jaundice might well have escaped notice for the first few days. In cases in which relief presumably was noted some time before jaundice was visible, it must be considered whether such remissions materially preceding jaundice were coincidental and unrelated to the subsequent jaundice or whether potent subclinical icterus was present. Further observations must determine whether the phenomenon can occur in the preicteric phase of jaundice, with low concentrations of serum bilirubin.

Completeness of Relief Provided by the Phenomenon.—Conservatism prompted the description of the reaction in the first report as "the analgesic effect of jaundice." Although relief of pain is the dominant effect, I believe that there is more to the phenomenon than analgesia. Stiffness and muscular spasm were notably relieved, soreness and tenderness were reduced and frequently even swelling was diminished materially. It must not be supposed, however, that residual periarticular thickening or stiffness, due to ankylosis or other structural damage, was reduced. The only symptoms affected were active inflammation in joints and only that amount of stiffness of joints which was due to active inflammation in and stiffness and spasm of surrounding muscles. Because these symptoms, as well as pain, were so frequently relieved, the analgesia must be regarded not as simple, merely a deadening of pained nerves, but of greater significance, an analgesia resulting from improvement in the underlying chemicopathologic state. Hence, "the inactivating effect of jaundice" was the term used later.[8]

Of the thirty-one patients, twenty-two (all those with fibrositis and 63 per cent of those with arthritis) obtained complete relief from pain and considered the disease symptomless. In seven cases of infectious arthritis, in one of lumbosacral and sciatic pain and in one of hypertrophic arthritis of the hips, relief was marked but incomplete.

Obviousness of the Phenomenon.—After my first report, criticism was offered that perhaps the patients had been permitted to answer leading questions in the manner desired by the questioner. In this regard, I may say that the earlier cases were discovered chiefly if not solely by me, but many of the patients of this second series first volunteered the

characteristic and revealing remarks to my associates in other departments of the clinic, some of whom were unfamiliar with this study. Most impressive were the remarks which patients made to persons who were not familiar with the phenomenon: relatives, friends or the local physician, who was unaware of it. These informative remarks were either voluntarily recounted or, at most, were the otherwise unguided answers to the question: "When you first noticed the effect you have mentioned, did you discuss it with those about you?"

The following selection of remarks provides evidence of the obviousness (and verity) of the phenomenon and of the perception of it by the patients:

1. A woman said: "When the jaundice came, to my surprise I found that I could do things with my joints that I hadn't been able to do for many months. It was a revelation to me, and when friends asked about my rheumatism I told them it had suddenly left me—for which I was very thankful." Concerning this patient, her physician wrote me: "Her arthritis disappeared through the back door as the jaundice came in the front door."[8]

2. A man said: "My rheumatism disappeared, although before the jaundice my neck was as stiff as if set in cement (from muscle stiffness).

3. A woman said: "Before the jaundice developed I had to let some of my housework slide. After the jaundice came, I did it all. I felt so well I didn't go to my doctor until two weeks after the jaundice came on."

4. A man said: "I would trade my rheumatism for jaundice any time if I could feel sure it wouldn't come back."

5. A woman said: "My wrists and fingers were badly swollen. I couldn't raise my arms or comb my hair. But within fourteen hours of the time the jaundice appeared [it lasted only three or four days], I could move all over. The swelling and stiffness left my hands. My joints didn't hurt for three weeks. Then the pains began to come back."

6. A man said to a relative: "What has become of my rheumatism?" To his local physician he said: "Since the beginning of this trouble [jaundice] I've hardly noticed I have rheumatism. I've had joint pains every day for two years, and I've never been so free from them as I am now."

7. A man said: "I told my brother-in-law that the only time I've really felt decent since the beginning of my rheumatism was when I had the yellow jaundice. I was very limber right after the jaundice. It was harvest time, and I worked the machinery easily."

8. A man said: "Since the jaundice came, the rheumatism has been cured. At least the jaundice has done that for me. The way to cure rheumatism is to give a fellow jaundice and then cure the jaundice!"

In spite of the general unreliability of testimonials and voluntary contributions of laymen, the following letter seems worthy of inclusion, as it affords further evidence of the obviousness and nature of the phenomenon as it occurred in the case of a hopelessly crippled patient (not listed in this series). The patient had come to the clinic in 1926, at the age of 16 years, with curvature and limitation of motion of the

entire spinal column due to marked spondylitis. Thereafter he had become progressively disabled, in spite of various treatments. In 1935, inspired by newspaper accounts of the beneficial effect of malarial fever on syphilis and of artificial fever on gonorrhea, he wrote to Dr. Melvin Henderson as follows:

> I have noticed in newspapers that one sickness may relieve another. I wish to report an experience I had in 1932. At that time I was almost completely disabled. I could only be stood on my feet to take sometimes none, sometimes as many as ten steps. Although I had taken no medicine except Kruschen salts occasionally, indigestion suddenly developed, without pain, perhaps from overeating. Four days later I noticed that my legs were less sore and more limber. On the fifth day my eyes were yellow and my urine was dark. I could stand on my feet, and my legs felt good. As the jaundice continued I could walk a few feet farther every day. The inflammation subsided in my worst joints. Most of the pain disappeared. In joints that were moderately affected, the stiffness was relieved. Although some of my joints were still completely stiffened, I was then able to shuffle 50 to 75 feet. The jaundice [apparently of moderate intensity] lasted one or two months. My joints were relieved for four to six months, then they slowly stiffened up again.

The letter concluded:

> Now [1935] I can be stood up but can't walk a step. My outlook is hopeless, and I want to offer myself for experimentation. . . . Since the discomfort of my indigestion was mild compared with the sore joints, I have often wished I could turn yellow as a pumpkin. I have frequently deliberately overeaten but have never found the right combination again. *In the explanation of this incident may lie the key to relief or cure of this disease.*

The statement is his; the italics are mine.

Although the majority of the patients recognized a connection between their remissions and the jaundice, as their remarks indicate, some noted the relief of symptoms but ascribed it to factors other than jaundice. Thus, the physician whose fibrositis was dramatically relieved, as previously noted herein (the representative case under the heading "Patients with Primary Fibrositis Which Was Relieved by Jaundice"), ascribed his relief to the baths which had given him practically no relief up to the first day of the appearance of jaundice. So, too, an arthritic woman with an abiding faith in the virtues of narcotics had cholecystic colic at 10 o'clock one morning. A hypodermic injection of morphine was given at 5 p. m. The next day she was jaundiced, and by night her arthritic pains (of five years' duration) had entirely left the shoulder and hands and had almost entirely left the knees. Later, the articular symptoms were completely relieved and remained so for three weeks, an effect she ascribed entirely to the single injection of morphine.

Relation Between the Degree of Symptomatic Relief and the Intensity and Duration of Jaundice.—The intensity and the duration of jaundice

are by no means always interdependent, but, in general, intense jaundice lasts longer than mild jaundice; hence the two factors are related and in these cases were definitely so. Thus, they can be considered together. All the patients with fibrositis received complete relief (for variable periods), although the jaundice of some was moderate and that of others was marked. Among the arthritic patients who were markedly but incompletely relieved of pain were some whose jaundice seemed to be as deep and as long continued as that of those whose pain was completely relieved. Several factors prevent establishment of definite correlation for this group of patients. There were too many variables: the duration, activity and extension of the arthritis, and the type, duration and intensity of the jaundice. Furthermore, some of the patients were not seen at the clinic until some time after the jaundice had cleared, and the intensity of the condition was not established definitely. Some patients came to the clinic while the jaundice was receding, and the previous maximal intensity of the jaundice could not be estimated. In spite of these difficulties, it seemed evident that the generalization made in the first report was essentially correct. The reaction was apparently quantitative. The concentration of serum bilirubin did not exactly parallel the completeness of the remission, but it seemed to have a relation thereto. "The zone of therapeutic effectiveness" seemed to begin generally at a level of about 8 to 10 mg. of bilirubin and to continue at levels above that concentration. This generalization will need to be modified if it can be shown that relief really does begin occasionally in the stage of subclinical jaundice.

Relation Between the Length of the Remission and the Intensity and Duration of the Jaundice.—The same factors that prevented deductions on the previous point interfered with conclusions on this point. In general, the longer and more intense the jaundice, the longer the remission. However, there was much variability. Thus, moderate jaundice of three weeks' duration was followed by a remission of only five weeks in one case and of three to four months in another. In still another case moderate jaundice of only ten days' duration was associated with marked (grade 3, not grade 4) relief for three or four months.

End Result of the Phenomenon.—With few exceptions, the effect of jaundice has proved to be temporary, not permanent. A lasting cure is not provided or to be expected. Nevertheless, the phenomenon has given such welcome relief of articular symptoms, such an impressive "vacation from rheumatism," that many have expressed themselves as being satisfied with the trade of rheumatism for jaundice and have wished the trade could be permanent. To fifteen (48 per cent) of the thirty-one patients, rheumatic symptoms and disability returned as before. To thirteen patients (42 per cent) the rheumatic symptoms returned but

in distinctly milder form. The subsequent courses in the remaining three cases were as follows: One patient died of cancer, one patient has not been heard from and one patient with fibrositis has had a remission which still continues after three years and nine months.

The symptoms of one patient who had severe arthritis returned only after ten months of complete relief, and those of another, after nineteen months of complete relief. Another arthritic patient had complete relief for a while, after which marked, although incomplete, relief persisted for two years; several of his previously affected joints are still asymptomatic, and only his shoulders hurt when he lies on them. Return of symptoms of fibrositis generally was delayed longer. Periods of jaundice for three to ten weeks induced the following complete remissions in cases of fibrositis for four and a half, five, six, eight and ten (in two cases) months, two years, three years and three years and nine months, respectively.

SPECULATIONS CONCERNING THE AGENT RESPONSIBLE FOR THE PHENOMENON

The agent responsible for the phenomenon and the mechanism whereby it acts have not been determined. Several possible agents have been considered. The responsible agent, substance x, may be a normal or an abnormal constituent of bile, or it may be a product of hepatic damage.

Bilirubin.—Obviously, in jaundice, bilirubin seems to be the most likely agent responsible for the effect. It might be argued that the tissues of arthritic patients lack sufficient bilirubin and that jaundice supplies the deficiency. This idea is particularly attractive in view of Race's [19] recent finding that the icterus index and the concentration of serum bilirubin are likely to be somewhat low among patients who have rheumatoid arthritis. Though the concentration of serum bilirubin of his patients who had rheumatic diseases was somewhat lower than that of the controls, the deficiency of bilirubin was small and was not the chief cause of the low icterus index.

There are several reasons why a hypothesis of deficiency of bilirubin of tissues has been unsatisfactory: First, remissions of the symptoms of arthritis may be induced by states other than jaundice, notably pregnancy, in which hyperbilirubinemia does not occur. Nature probably does not cure arthritis even temporarily in two totally different ways; in the last analysis, the agent responsible for the relief of arthritic

19. Race, Joseph: Biochemical Investigations in Chronic Rheumatic Diseases, in Reports on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1935, no. 1, pp. 55-71; Vitamins and Rheumatic Diseases, in Reports on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1937, no. 3, pp. 30-48.

symptoms probably is the same in the presence both of pregnancy and of jaundice, although the mechanism for developing the agent is different. Second, in respect to the jaundiced arthritic patients, the relation between the depth of the jaundice (the concentration of serum bilirubin) and the phenomenon of symptomatic relief, although close, was not absolute. In many cases the analgesia lasted long after the serum bilirubin (and presumably the tissue bilirubin) content had returned to normal. Furthermore, if the statements of the patients who noted relief before the onset of visible jaundice are reliable, they indicate that hyperbilirubinemia was not necessary or that only slight hyperbilirubinemia was necessary to produce the phenomenon. Since other observations on the ineffectiveness of slight, even if definitely visible, jaundice (5 to 8 mg. of serum bilirubin) have made the latter deduction untenable, no final conclusion as to the role of bilirubin can now be made. The phenomenon occurs consistently in the presence of fairly intense hyperbilirubinemia but is generally absent when hyperbilirubinemia is not present or is only slight. This seems to incriminate bilirubin, but if the mechanism of relief in pregnancy is ultimately the same as in jaundice, one must conclude that an amount of bilirubin that will produce icterus is not necessary for the phenomenon. Perhaps in the presence of pregnancy and of jaundice, a special potent form of bilirubin, a derivative of bilirubin (and not "ordinary bilirubin") or perhaps an allied compound, is the responsible agent and is effective even in amounts that do not cause pigmentation.

Bile Salts.—These may be the responsible agents. In certain types of hepatic disease accompanied with jaundice, the content of bile salts presumably is increased in the blood, but in other types of hepatic disease accompanied with jaundice it is apparently decreased. Until adequate methods for determination of bile salts in the blood are available, opinion on the possible connection between bile salts and the phenomenon under discussion must be held in abeyance.

Hepatic Autolysate.—A product of hepatic injury, some hepatic autolysate, may be the responsible agent. Snell [20] has said that he inclines to this view. I hope the responsible agent is something simpler to identify than a hepatic autolysate. It seems more likely to me that the responsible agent is some product which is normal, not abnormal, to the tissues helped thereby.

Special Diet.—One of Pemberton's [21] patients (his case 53) apparently experienced the phenomenon in the course of jaundice, but the

20. Snell, A. M., cited by Hench.[8]

21. Pemberton, Ralph: Studies on Arthritis in the Army, Based on Four Hundred Cases: V. Roentgen-Ray Evidences, Clinical Considerations, Treatment, Summary, Conclusions and Clinical Abstracts of Cases Studied [Case 53], Arch. Int. Med. **25**:398 (April) 1920.

relief was ascribed to the dietary restrictions incident to jaundice. The phenomenon cannot be attributable to the coincidental use of a diet low in calories or in carbohydrate. Many of the patients while in the hospital under the care of Drs. Snell, Weir, Comfort, Wilbur and myself were given 400 to 500 Gm. of carbohydrate daily (bread, cereals, potatoes, crackers, jellies, cakes, fruit juices and candy between meals). They were on this so-called supportive diet for hepatic disease for three to five weeks in the hospital and for at least three to six months thereafter. While in the hospital they were generally given also an average of 100 Gm. of sugar intravenously daily for three weeks. Glycosuria often was produced, but the analgesia and reduction of stiffness and swelling of joints were in no way disturbed by this large intake of carbohydrate daily for many weeks.

SPECULATION CONCERNING CIRCUMSTANCES THAT MIGHT BE RESPONSIBLE FOR THE PHENOMENON

It has been suggested that the responsible factor is not a chemical substance but a set of circumstances incident to jaundice: simple sedation, rest and reduction of trauma, dehydration and counterirritation.

Simple Sedation.—It has been argued that perhaps one of the chemical compounds concerned in some way with jaundice is a sedative substance, nonspecific for rheumatism, which dulls the sensorium and diminishes perception of pain by the markedly jaundiced patient. This explanation is not satisfactory, because the phenomenon often includes reduction of stiffness and swelling as well as analgesia. Furthermore, the majority of these jaundiced arthritic patients are physically and mentally active and alert, in spite of the jaundice, as photographs and my motion pictures of them indicate. If jaundice provides simple nonspecific analgesia, it would probably have been noted previously in association with many diseases. As far as I am aware, it has not been noted that visceral pains with jaundice are, in general, any less severe than those without jaundice. Were simple general analgesia provided, one of the gouty patients (case 5, table 3), the patient with the painful sternoclavicular swelling (case 9) and the one with the ischemic neuritis (case 13) should have obtained some relief or more relief than they did, because the jaundice they had was fairly intense and the level of the serum bilirubin was in the "zone of therapeutic effectiveness."

Rest; Reduction of Trauma.—It has been suggested that rest in bed or a sharp reduction of activity and of trauma to joints in the course of jaundice was responsible for the relief of pain. Rest cannot be responsible for the effect, because, although some patients remained in bed during the early stages of jaundice, most of them, freed from pain during jaundice, were from the onset of jaundice not less active but more active than ever, as their statements indicate.

Counterirritation.—It has been suggested that jaundice provided a form of counterirritation, that the patients were too sick with jaundice to notice the joints. On the contrary, most of them noticed the joints particularly, by reason of the degree of articular relief obtained.

Dehydration.—Dehydration is said to afford some relief to the patient who has chronic arthritis.[22] I do not believe dehydration was responsible for the phenomenon of relief. Dehydration was generally not noticeable. Indeed, a large amount of fluid was generally given, not because the patients were dehydrated but to combat toxicity; and analgesia continued in spite of this.

SPECULATIONS CONCERNING THE MECHANISM WHEREBY THE AGENT MAY ACT

Assuming that the responsible agent is a specific chemical substance or a combination of substances and not a nonspecific set of circumstances, it may be suggested that the phenomenon results from (1) the correction of some chemical deficiency, (2) the correction of some chemical oversufficiency or (3) a process of bacteriolysis, bacteriostasis or detoxification.

1. As has been mentioned, it is an attractive idea that jaundice provides to the general circulation and to the tissues involved in arthritis a normal chemical constituent, not an abnormal product, adequate amounts of which patients with arthritis or fibrosis did not previously possess. The validity of this idea remains to be proved.

2. Another working hypothesis might be based on a contrary point of view: Damage to the liver may temporarily interfere with the production of some substance of which the rheumatic patient has a pathologic oversupply. Thus, the hepatitis with jaundice may correct some hyperfunctioning, not hypofunctioning, state. If this were so, should not severe hepatitis alone, without jaundice, be able to invoke the phenomenon? As noted in my first report, the phenomenon did not appear in one case (case 17) in which marked cinchophen hepatitis developed without jaundice.

3. A third hypothesis is that "substance x" may have a power of detoxification or a bacteriolytic or bacteriostatic effect on organisms responsible for chronic rheumatism. Bile in certain concentrations is bacteriolytic to pneumococci, and it has recently been suggested [23] that

22. Scull, C. W., and Pemberton, Ralph: The Influence of Dietetic and Other Factors on the Swelling of Tissues in Arthritis: Preliminary Report, Ann. Int. Med. **8**:1247-1265 (April) 1935.

23. Najib-Farah: Defensive Rôle of Bilirubinaemia in Pneumococcal Infection, Lancet **1**:505-506 (Feb. 22) 1937.

the jaundice seen in certain cases of pneumonia represents a protective mechanism. As applied to pneumonia, the idea seems more ingenious than sound, in the absence of data indicating that patients who have pneumonia and in whom jaundice develops recover more readily than nonjaundiced patients who have pneumonia. Suffice it to say, the bacteriologists among my colleagues, carrying on certain preliminary investigations, have failed to note bacteriolysis or bacteriostasis for various arthrotropic, neurotropic or neuromyotropic streptococci in vitro, although they have used concentrations of bilirubin and bile acids, alone and separately, equal to or greater than the concentrations present in clinical jaundice. Nor have they noted definite increases in streptococcic antibodies in a few of the cases of jaundice accompanying arthritis. Furthermore, several of the jaundiced arthritic patients obviously had not been "sterilized" of their arthrotropic streptococci, for these organisms still could be isolated from the nasopharynx or other foci, even in the presence of the phenomenon. Further speculation is useless at present, and I have no idea which theory of the cause of arthritis or fibrositis these investigations will support.

THERAPEUTIC IMPLICATIONS

The therapeutic implications of this phenomenon seem obvious. An intensive study of it may lead to a better understanding of the pathogenesis of rheumatic diseases and perhaps of the general mechanisms of immunity, or, more important, it may lead to a method of "curing" these diseases or at least of controlling their activity. Jaundice, obviously, provides not a cure but a temporary control, at least, of symptoms. But is it not likely that the differences between a preliminary temporary remission and the final permanent remission or cure are merely quantitative—differences of degree and of persistence? As has been stated before, it would be gratifying if one were able to repeat nature's dramatic (if accidental) method of control, to induce at will, repeatedly if necessary, a similar remission of symptoms by the use of some nontoxic accompaniment of jaundice, effective in available concentrations.

ATTEMPTS TO REPRODUCE THE PHENOMENON

In attempting to reproduce the phenomenon for research on the treatment of arthritic patients, various methods of approach were considered. It was decided to administer to patients who wished to cooperate in the investigation the different available constituents of bile, first alone and then in combination; first by the simpler routes (oral and rectal) and later intravenously or otherwise. Because of the cost and relative unavailability of bilirubin at the time the investigation was under way, other substances were used first.

Bile Salts.—A number of essentially similar preparations are available. One preparation [24] was given by mouth in doses up to 112 tablets (total 224 grains [14.6 Gm.]) in fourteen days. Ox bile was given in doses up to 890 grains (57.8 Gm.) in thirteen days. These are equal to or above the usual doses prescribed. The results were questionable: Some arthritic patients felt partially relieved; others were unaffected. Obviously the complete phenomenon provided by spontaneous jaundice was not being reproduced by these small doses of bile salts. Rather than persist in their use, it was decided to postpone further investigations with them and to progress to other methods in an attempt to obtain the full effect comparable to the phenomenon described, not the slow, indefinite type of improvement which current methods already provided.

Synthetic Bile Salts.—The sodium salt of dehydrocholic acid (decholin sodium) was administered intravenously, by mouth and in combination. One ampule (2 Gm.) was given to each of several patients with arthritis or with fibrositis intravenously daily for from eight to twenty-one days. The tablets, each of 3¾ grains (0.25 Gm.), were given orally in doses up to a total of 178 tablets (667.5 grains [44.5 Gm.]) in twenty-one days. Decholin was given by Lebermann [25] to one patient with acute articular rheumatism, with reported benefit. It has also been used by others in the study of the hepatic function of patients with chronic arthritis.[26] The results noted by my patients were variable, in the main, being negative. Some believed their pains were partially relieved; but, as with the previous preparation, it seemed evident that the ordinary doses of this preparation given alone would not precipitate the complete phenomenon. This was also the tentative conclusion of Sidel.[27]

Diluted Ox Bile.—Variable amounts of sterile ox bile diluted in water and olive oil were administered by proctoclysis but proved irritating and were promptly evacuated.

Human Bile.—It was frankly believed that administration of bile or its constituents by the oral or by the rectal route would be of no therapeutic value, since administration of bile products by these routes could not be expected to increase materially their concentration in the general blood stream. The administered substances, if absorbed, probably would pass only through the enterohepatic circulation and would

24. The preparation used was glychotauro, which is manufactured by Hynson, Westcott & Dunning, Baltimore.

25. Lebermann, Ferdinand: Klinische Erfahrungen mit "Decholin," Fortschr. d. Med. **44**:703-704 (July) 1926.

26. Rawls, W. B.: Liver Function in Rheumatoid (Chronic Infectious) Arthritis: Preliminary Report, Ann. Int. Med. **10**:1021-1027 (Jan.) 1937.

27. Sidel, Nathan: Personal communication to the author.

never reach the general (or articular) circulation. Nevertheless, Dr. Winfield Butsch procured a fairly large quantity of human bile which had drained from a T tube and which was free from pathogenic organisms and administered it to a few of my arthritic patients. Amounts of human bile up to 2,600 cc. in one day (7,650 cc. in ten days) were given by stomach tube. The concentration of serum bilirubin was not increased, and relief from articular symptoms was not noted. Contrary to expectation, these amounts of "heterologous bile" did not produce any gastro-intestinal symptoms. Indeed, one patient took it with pleasure, saying it increased his appetite.

Liver Extract.—Occasionally I have used commercial preparations of liver extract in the treatment of arthritic patients with secondary or with coincident pernicious anemia. The use of such preparations in ordinary amounts seemed to have no marked effect on articular symptoms, certainly none similar to the phenomenon characteristic of spontaneous jaundice. This also has been the experience of Dr. George Minot [28] and of Dr. William Murphy.[29] Therefore, this method of approach has not been extensively repeated.

Transfusions of Highly Jaundiced Blood.—In the hope that "substance x" might be present in potent amounts in portions of jaundiced blood available for transfusion, four arthritic patients were given from one to four such transfusions. To my knowledge, jaundiced blood has not heretofore been deliberately used for transfusion. Because Dr. Lundy and I were uncertain of its effects, small doses were first given, and only persons of identical blood groups were used as donor and recipient. What I called round-robin transfusions were arranged. Nonarthritic jaundiced patients, suffering from a variety of hepatic disorders, whose blood showed a negative Wassermann reaction and was sterile, were willing to cooperate, giving an amount of their "bad blood" for twice as much "good blood" from a healthy professional donor, at no expense to the patients. The jaundiced blood was injected into nonjaundiced arthritic patients in the usual manner. One patient, for her fourth transfusion, received 800 cc. of jaundiced blood, the concentration of serum bilirubin being 21 mg. per hundred cubic centimeters. Thus, only a relatively small amount of bilirubin was actually injected; namely, 168 mg. In general, there was no reaction or only the usual slight reaction, as from any transfusion. During the completion of this large transfusion, extensive hives developed, and there was a distinctly yellow tinge to the skin. The next day she insisted she had less pain; if so, relief was transient, and the serum bilirubin content was slightly but not materially, increased.

28. Minot, George: Personal communication to the author.

29. Murphy, William P.: Personal communication to the author.

Artificially Produced Jaundice.—Obviously, other methods of approach were necessary if an adequate amount of the hypothetic agent was to be provided. Methods of inducing relatively harmless jaundice were sought. Single doses of as much as 500 mg. of bilirubin, injected intravenously, are excreted rapidly and are (or were) expensive [30] and ineffective. Both cinchophen and neoarsphenamine produce jaundice inconsistently, they are not controllable in their effect and their use may have serious consequences. Simple catarrhal jaundice does not seem subject to experimental reproduction. The tropical types of jaundice are dangerous or unsuitable.

In spite of all difficulties, it became evident that a reproducible, relatively harmless type of jaundice was required in order to study the phenomenon adequately. A poor mosaic was being provided by the patchwork chemical investigations accomplished with the cooperation of patients who had spontaneous jaundice; none of them lived near Rochester, so they usually had to go home just when desirable chemical studies were being made. Chemical analyses made on samples of their blood mailed to the clinic were of uncertain value. To study the intricacies of the phenomenon, one should study the changing physiologic and chemical processes in different phases: before the period of jaundice, in the preicteric stage, as jaundice becomes visible and the phenomenon becomes apparent, as jaundice fades and disappears but analgesia persists, and finally when reactivation of the disease occurs.

Toluylenediamine Jaundice.—The studies of Wolff,[31] McGowan,[32] and McGowan, Bollman and Mann [33] suggested that toluylenediamine might be a suitable substance to use in the first attempts deliberately to induce jaundice in a volunteer arthritic patient. Toluylenediamine jaundice in animals was intense, it was somewhat controllable, it was of intrahepatic type, and after jaundice had disappeared the results of hepatic function tests returned to normal, and there was no pathologic evidence of significant damage to the liver. Recognizing the possible risk, a discouraged arthritic patient (fig. 3), thoroughly disgusted with results she had obtained from an amazingly long series of orthodox, and unorthodox, measures employed over a period of thirteen years, elected to take toluylenediamine orally (June 1936). I was particularly fortunate in

30. At the time the work was being done the cost was $25 a gram.

31. Wolff, H. J.: The Physiologic Action of Toluylendiamin and Its Relation to Experimental Jaundice, J. Pharmacol. & Exper. Therap. **50**:407-419 (April) 1934.

32. McGowan, J. M.: Bile Salts in Toluylenediamine Jaundice, Proc. Staff Meet., Mayo Clin. **10**:565-567 (Sept. 4) 1935.

33. McGowan, J. M.; Bollman, J. L., and Mann, F. C.: The Bile Acids in Icterus Produced by Toluylenediamine, J. Pharmacol. & Exper. Therap. **58**:305-311 (Nov.) 1936.

the selection of this patient, because annoying gastro-intestinal irritation was induced, only slight jaundice was obtained (and that with some difficulty) and the jaundice was ineffectual against the pain. Nevertheless, the woman cooperated remarkably and accepted the failure philosophically. The details of this case will be reported separately in another paper.

Contrary to expectation, the jaundice induced was wholly of the hemolytic type. With extreme caution the patient was carried to an erythrocyte count as low as 1,530,000 per cubic millimeter of blood and to a concentration of hemoglobin of 5.2 Gm. per hundred cubic centimeters. The color of the eyes and skin was lemon, not orange; the jaundice was transient and rather mild, and the maximal concentration of serum bilirubin was only 6.3 mg. (direct reaction), never entering

Fig. 3.—One hand and both feet of a patient who had had severe chronic infectious arthritis for thirteen years. One may note deformities of the fingers and toes and swelling of the ankles, especially of the left ankle. Mild "experimental jaundice," which was induced with toluylenediamine, was not associated with remission of articular symptoms.

the "zone of therapeutic effectiveness." Subsequently, two transfusions and other hematonics were given, and the woman made a rapid and uneventful recovery as far as the blood was concerned. Results of tests showed that the hepatic and renal functions either were normal or had returned promptly to normal.

Some more feasible method of studying the phenomenon, a method perhaps adaptable to the field of therapy, is needed, but when it is obtained it should not be regarded as an end but only as a means to an end. Therapeutic jaundice may be an attractive term, but even if successfully induced, it should be, at best, considered a crude form of treatment, just a step—but an important one—on the way to the refined therapy of the future.

SUMMARY AND CONCLUSIONS

Further observations have been made on the analgesic or the inactivating effect of jaundice on chronic infectious (atrophic, rheumatoid) arthritis, on primary fibrositis and on certain types of lumbosacral and sciatic pain. Clinical and chemical studies have been made on a new series of thirty-one patients whose rheumatic symptoms were partially or, generally, completely relieved coincident with the onset of spontaneous jaundice. With the addition of the fourteen patients reported on in the first series, a total of forty-five patients have experienced this phenomenon: twenty-eight with chronic infectious (atrophic) arthritis, twelve with primary periarticular and intramuscular fibrositis, four with lumbosacral or sciatic pain and one with hypertrophic arthritis localized in the hip joints. Various types of jaundice appeared to be equally effective: intrahepatic jaundice from cinchophen, spontaneous intrahepatic jaundice of the catarrhal or epidemic infectious type, intrahepatic jaundice associated with hepatitis and cirrhosis, and obstructive jaundice from stones or from a malignant growth. No opportunity to study the effect of marked hemolytic jaundice has presented itself.

The phenomenon was dependent more on the quantity than on the quality of jaundice. The concentration of serum bilirubin served as a general index of the effectiveness of the phenomenon, and what I have called the zone of therapeutic effectiveness has been established tentatively as beginning at a concentration of serum bilirubin of about 8 to 10 mg. per hundred cubic centimeters. However, certain data are at hand which suggest that the concentration of bilirubin in jaundice may not be the chief or sole factor in producing the phenomenon.

The phenomenon was characterized by the dramatic promptness of its appearance, its notable obviousness and the completeness of its effect. The duration of the remissions induced by jaundice bore a general but not a specific relation to the intensity and duration of the coincident jaundice. The analgesic effect of jaundice was noted generally within the first three days of visible jaundice. Of the thirty-one new patients who experienced analgesia, twenty-two (71 per cent) received complete relief, and nine (29 per cent) received partial but almost complete relief. All nine patients with fibrositis and 63 per cent (twelve) of the nineteen arthritic patients were relieved completely, although temporarily, of all rheumatic symptoms.

Significant jaundice precipitated a remission, apparently not a cure, of the diseases under consideration, but the remissions provided "vacations from rheumatism" which were gratefully received by the patients, most of whom would have preferred to make permanent the trade of the new condition for the old. The remission of articular and muscular symptoms lasted from three weeks to forty-five months; in general, they lasted several weeks. The arthritic patients were relieved of symptoms

for an average of about four months, and the patients with fibrositis, for an average of about five months. The remissions lasted roughly about twice as long as the jaundice, but because of variable factors, this is a generalization not applicable to individual cases.

In the majority of cases the rheumatic symptoms returned to their previous intensity, but in 42 per cent of the cases the symptoms recurred in milder form and have so remained.

A study of thirteen additional new patients (four with atrophic arthritis and nine with articular or neuritic symptoms resulting from conditions other than atrophic arthritis or primary fibrositis) who did not experience analgesia in the presence of jaundice of varying intensity indicated the relative specificity of the reaction and its closer relation to the quantity than to the quality of jaundice. Painful gouty arthritis, post-herpetic neuralgia, ischemic neuritis, juxta-articular metastasis and arthralgia of a special type were unrelieved in the presence of jaundice which at times reached the so-called zone of therapeutic effectiveness.

The therapeutic implications are obvious. The responsible agent and the mechanism whereby it acts are as yet unknown. Some working hypotheses have been developed. Attempts to reproduce the phenomenon, for investigative rather than for immediate therapeutic purposes, were made. They included the administration of whole bile and certain of its constituents by various routes. Natural and synthetic bile salts (decholin) were given. Bile was fed by stomach tube. Transfusions of deeply jaundiced blood were tried. Jaundice was produced by the administration of toluylenediamine. The clinical and chemical results of these methods were studied; by these means and with the rather small doses used, the phenomenon has not yet been reproduced.

For an adequate study of the phenomenon, the development of a method to produce suitable artificial jaundice may be required. However, when it is accomplished, artificial or "therapeutic" jaundice should be regarded not as an end in itself but only as a means to an end. Two conclusions seem permissible:

1. Chronic infectious (atrophic, rheumatoid) arthritis and primary fibrositis are not necessarily relentless, uncontrollable diseases. Their pathologic physiology is more completely and more rapidly reversible than has been supposed heretofore.

2. Nature possesses a highly effective method of quickly stopping the disease for a while and of producing a dramatic remission; this phenomenon is precipitated more rapidly and more completely by jaundice than by any other known physiologic change or therapeutic method. It behooves physicans to discover this antidote and the mechanism of its action.

The discussion of this paper appears in conjunction with that of the following paper, by Drs. Thompson and Wyatt.

EXPERIMENTALLY INDUCED JAUNDICE (HYPERBILIRUBINEMIA)

REPORT OF ANIMAL EXPERIMENTATION AND OF THE PHYSIOLOGIC EFFECT OF JAUNDICE IN PATIENTS WITH ATROPHIC ARTHRITIS

HARRY E. THOMPSON, M.D.
AND
BERNARD L. WYATT, M.D.
TUCSON, ARIZ.

Since the publication of the article by Hench,[1] in 1933, in which it was noted that intercurrent jaundice may evoke a remission of chronic atrophic arthritis and fibrositis, we have been actively interested in the experimental production of jaundice. The observations of Hench have been confirmed by Sidel and Abrams [2] and by Hench.[3] We have studied three patients with atrophic arthritis in whom jaundice occurred. Jaundice occurred in two of these patients after toxic hepatitis, in one case due to neocinchophen (30 grains [2 Gm.] daily for sixteen days) and in the other case to neocinchophen (12 grains [0.8 Gm.] daily for twenty-four days) and oxo-ate B (calcium ortho-iodoxybenzoate, 15 grains [1 Gm.] daily for twenty days). In one patient no effect on the arthritis was noted (the serum bilirubin content was not determined), but the other patient, with the onset of jaundice, was relieved of pain. During the jaundice, which lasted thirty days, the articular symptoms were entirely relieved. The serum bilirubin level for this patient was 24 mg. per hundred cubic centimeters. With the disappearance of the jaundice the pain returned slightly; however, she continued fairly free from manifestations for three years. The arthritis then returned with

Presented in part before the Fifth Conference on Rheumatic Disease held by the American Rheumatism Association, Atlantic City, N. J., June 7, 1937.

1. Hench, P. S.: Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis and Sciatic Pain, Proc. Staff Meet., Mayo Clin. **8**:430 (July 12) 1933.

2. Sidel, N., and Abrams, M. I.: Jaundice in Arthritis: Its Analgesic Action, New England J. Med. **210**:181 (Jan. 25) 1934.

3. Hench, P. S.: The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, Ann. Int. Med. **7**:1278, 1934; A Clinic on Some Diseases of the Joints: IV. The Inactivating Effect of Jaundice in Chronic (Infectious) Arthritis and Fibrositis, M. Clin. North America **19**:573, 1935.

severity. The third patient (referred by Dr. R. A. Hicks) was a girl aged 3½ years. Nine months previously, severe polyarticular arthritis of the atrophic type developed. The joints of the fingers, wrists, elbows, knees, ankles and neck were involved, with marked limitation of motion, heat, swelling and pain. Five blood transfusions of 275 cc. each were given in five weeks. After the last transfusion a severe reaction occurred, with chills and repeated emesis at three to four hour intervals for twelve hours. Jaundice appeared the following morning (grade 3+; serum bilirubin content, 12 mg.) and persisted for approximately five days. Hemoglobinuria appeared and remained for three days after the reaction. With the onset of jaundice the swelling and pain diminished, the arthritis completely disappeared and the child remained well for sixteen months, after which the symptoms returned with less severity.

This case is of interest because the jaundice was accompanied with a severe posttransfusion reaction, marked destruction of red blood cells and hemoglobinuria. Although it may be questionable whether this was hemolytic jaundice, the case is included here because the jaundice was followed by a remission of the arthritis.

Bile contains four main components:[4] (1) bile pigments, (2) bile salts, (3) lipoid constituents and (4) mucin. It has been generally observed[5] that of this group, the bile pigments alone reach relatively higher levels in the circulation in jaundice of the hemolytic type and that both bilirubin and bile salts show higher levels in jaundice of the obstructive and toxic type. Although the majority of the instances reported in the literature indicate that in the cases of jaundice in which the most beneficial effect was noted there was an accompanying rise in the levels for serum bilirubin and bile salts, these two substances cannot be considered entirely responsible, since we have observed a remission following jaundice (third case) in which the level of bile salts presumably was not raised. Hence, we determined the effects of bile pigments alone, of bile salts alone and of bile pigments and bile salts in combination. There was no apparent reason for determining the effect of the other constituents of bile, as they are not involved. We have observed that the serum bilirubin levels[6] are lower for patients with

4. Wright, S.: Applied Physiology, ed. 4, New York, Oxford University Press, 1932, p. 418.

5. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931.

6. The method of Ernst and Förster gives higher values than the quantitative van den Bergh test, as the comparison of colors is direct and measures other pigments as well as bilirubin. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blutbilirubins, Klin. Wchnschr. **3**:2386, 1924.

chronic atrophic arthritis than for normal persons (table 1). These findings confirm the observations made by Race.[7]

We studied the effect of single and of repeated intravenous injections of bilirubin at various levels of dosage in rabbits. The results may be briefly summarized as follows: 1. Bilirubin was rapidly excreted after single intravenous injections. 2. Repeated injections of 20 mg. of bilirubin per kilogram of body weight daily for ten days produced chronic bilirubinemia and retention of the pigment in the tissue. 3. No

TABLE 1.—*Serum Bilirubin Values* for Patients with Chronic Atrophic Arthritis and for Normal Persons*

Patients With Chronic Atrophic Arthritis			Normal Persons	
Number	Red Blood Cells, Millions per Cu. Mm.	Serum Bilirubin, Mg. per 100 Cc.	Number	Serum Bilirubin, Mg. per 100 Cc.
1	4.20	0.36	1	2.06
2	4.10	1.58	2	2.07
3	4.85	1.63	3	2.76
4	4.80	1.50	4	1.98
5 †	4.50	2.24	5	1.72
6	4.40	1.70	6	1.70
7	4.38	1.69	7	1.84
8	4.91	1.70	8	2.39
9	4.85	1.78	9	2.07
10	4.50	1.04	10	2.22
11	4.98	2.01	11	2.51
12	4.79	1.66	12	2.23
13	4.82	1.69	13	2.10
14	4.60	1.60	14	1.94
15	4.96	1.56	15	2.10
16	4.50	1.50	16	1.99
17	4.53	1.67	17	1.91
18	4.51	0.88	18	1.99
19	4.68	0.90	19	2.05
20	4.35	1.10	20	2.08
21	4.54	0.67	21	1.94
22	4.60	0.63	22	1.98
23	4.55	0.94	23	2.03
24	4.79	1.50	24	1.89
25	4.61	1.28	25	2.00
Averages		1.39		2.06

* The Ernst-Förster method was used.
† This patient had chronic atrophic arthritis and coronary thrombosis.

toxic effects were noted during the administration or at autopsy. 4. The single fatal dose of bilirubin was 175 to 200 mg. per kilogram. These findings indicated that the excretion of bilirubin was rapid, even with repeated doses but that the tissue took up sufficient pigment so that slight bilirubinemia persisted.

Three patients with chronic atrophic arthritis were given a series of repeated injections of bilirubin in doses of 10 to 15 mg. per kilogram daily. Observations on these patients demonstrated that bilirubin is rapidly but not completely excreted from the blood after repeated injec-

7. Race, J.: Biochemical Investigations in Chronic Rheumatic Diseases, in Report on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1935, no. 1, p. 61.

tions. Slight hyperbilirubinemia developed, and there was sufficient retention in the tissues to produce icterus (table 2 and chart 1). Little or no symptomatic improvement was noted in this group.

It should be mentioned here that many investigators [8] have injected bilirubin into patients as a test of hepatic function or for other purposes, but no mention has been made of the effect of this substance on the symptoms of atrophic arthritis.

We then tried the administration of bile salt alone (decholin sodium) to ten patients with chronic atrophic arthritis. They were given intravenously 2 Gm. of the salt daily for nine to twelve days. Little or no symptomatic improvement was noted. This is confirmatory of the results of Hench.[9]

The next step was the employment of bilirubin and bile salt together.

The animal experiments were repeated, using bilirubin at 20 mg. per kilogram and the sodium salt of dehydrocholic acid [10] in doses of 40 mg.

8. (*a*) von Bergmann, G.: Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, Klin. Wchnschr. **6**:776, 1927. (*b*) Eilbott, W.: Funktionsprüfung der Leber mittels Bilirubinbelastung, Ztschr. f. klin. Med. **106**:529, 1927. (*c*) Harrop, G. A., Jr., and Barron, E. S. G.: The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function, J. Clin. Investigation **9**:577, 1931. (*d*) Soffer, L. J.: Bilirubin as a Test for Liver Function During Normal Pregnancy, Bull. Johns Hopkins Hosp. **52**:365, 1933. (*e*) Soffer, L. J., and Paulson, M.: Residual Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, Arch. Int. Med. **53**:809 (June) 1934. (*f*) Rosenthal, S. M.: Modern Methods of Testing Liver Function, M. Ann. District of Columbia **1**:294, 1932. (*g*) Ruhbaum, W. N., and Matheja, W.: Leberfunktionsproben bei latenter Leberschadigung, Klin. Wchnschr. **14**:1568, 1935. (*h*) Fulde, W.: Wert und Methodik verschiedener Leberfunktionsprüfungen für Klinik und Praxis, ibid. **14**:1201, 1935. (*i*) Kalk, H.: Klinische Untersuchungen über die Frage des latenten Leberschadens, Deutsche med. Wchnschr. **58**:1078, 1119 and 1160, 1932. (*j*) Dragstedt, C. A., and Mills, M. A.: Bilirubinaemia and Bromsulphalein Retention, Proc. Soc. Exper. Biol. & Med. **34**:467, 1936. (*k*) Takane, S.: Ueber den Einfluss verschiedener Narkosemittel auf die Leberfunktion: Experimentelle Untersuchungen mit Bilirubin und Kongorot, Arch. f. klin. Chir. **170**:672, 1932. (*l*) Scholderer, H.: Disappearance of Injected Bilirubin from Blood Stream, in Cameron, A. T., and Gilmour, C. R.: The Biochemistry of Medicine, London, J. & A. Churchill, 1933. (*m*) Rabinowitch, I. M.: Renal Threshold of Bilirubin, J. Biol. Chem. **97**:163, 1932. (*n*) Saiki, Sanetoshi: Experimental Investigation on the Fate of Bilirubin Introduced into the Blood Vessels, Jap. J. Gastroenterol. **2**:203, 1930; **3**:1, 119, 123, 192, 195, 197 and 203, 1931. (*o*) Marengo, G., and Massimello, F.: Der Einfluss der Tachidrolo-Decholin-Mischspritze auf die Bilirubinämie und die Diurese, Arch. f. exper. Path. u. Pharmakol. **178**:486, 1935. (*p*) Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile, J. Biol. Chem. **78**:691, 1928. (*q*) Elliott, C. A., and Nadler, W. H.: Diseases of the Liver, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 7, p. 80.

9. Hench, P. S.: Personal communication to the authors.

10. Decholin sodium was obtained from Riedel-de Haen, Inc., New York.

TABLE 2.—*Serum Bilirubin Values After Repeated Intravenous Injections of Bilirubin Alone*

		Serum Bilirubin, Mg. per 100 Cc.*															
		1 Injection		2 Injections		3 Injections		4 Injections		5 Injections		6 Injections		After Last Injection			
Case No.	Normal Value	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	2 Days	4 Days	7 Days	15 Days
1	0.88	10.78	0.99	8.43	0.89	15.12†	1.93	....	2.17	....	2.38	5.34‡	2.83	2.60	2.10	....	1.30
2	0.67	11.96	1.83	13.46	2.14	12.00	2.59	15.1	2.51	....	2.51	....	....	2.21	2.00	1.50	1.00
3	0.63	12.15	1.01	12.00	1.39	14.71	3.37	....	....	....	....	....	....	2.52	1.80	0.98	....

* The Ernst-Förster method was used.
† The dose employed was 15 mg. per kilogram.
‡ The dose employed was 5 mg. per kilogram.

per kilogram. This bile salt was selected as it is apparently less toxic intravenously than some other bile salts.[11] In addition to the previous research, we studied the functional capacity of the liver (bromsulphalein test).

A brief summary of this study is as follows: 1. In single doses the clearance of bilirubin was essentially the same with bile salt as with bilirubin used alone. 2. With repeated administration there appeared a slightly greater retention of pigment in the blood and tissues when bile salt was added to the bilirubin. 3. No evidences of toxicity appeared during or after the administration or at autopsy.

A patient having chronic nonspecific atrophic arthritis was selected. He was given daily doses of 10 mg. of bilirubin per kilogram intravenously for four days, and on the fifth, sixth and seventh days 40 mg. of decholin sodium per kilogram was added to the infusion. This was

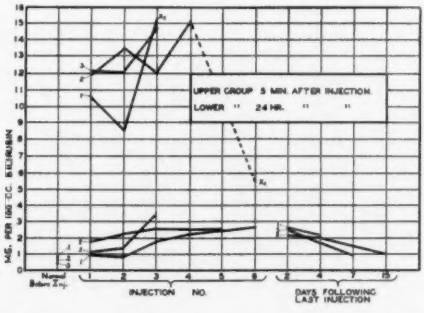


Chart 1.—The clearance of bilirubin from the blood stream after repeated injections of bilirubin (10 mg. per kilogram). X_2 indicates 5 mg. and X_3, 15 mg. of bilirubin per kilogram.

done in order to contrast the effects of bilirubin alone with the effects of bilirubin and bile salt combined. After four injections of bilirubin, slight icterus developed, but no relief of symptoms was noted, both knees and one ankle remaining warm, swollen and painful. However, within eight hours after the fifth infusion (bilirubin and bile salt), marked relief from pain in all the involved joints appeared. He stated that for the first time in six months he had slept entirely through the night without being awakened by pain. In addition, the swelling of the joints had diminished slightly, and he was more icteric. The serum

11. Weigand, F. A.: Diuretic Action of Intravenous Sodium Dehydrocholate, J. A. M. A. **105**:2034 (Dec. 21) 1935. Steiner, R. F.; Bartle, H. J., and Lyon, B. B. V.: The Cholagogue Effect of the Intravenous Injection of Sodium Dehydrocholate with a Résumé of the Literature on Bile Salt Metabolism, Am. J. M. Sc. **182**:822, 1931.

bilirubin content twenty-four hours after this infusion was 2.81 mg. per hundred cubic centimeters (chart 2, case 1). The van den Bergh reaction was indirect. After the two succeeding injections the articular swelling rapidly diminished, and the analgesia has persisted up to the time of writing (five months). This reversal of symptoms came on so dramatically and suddenly that one immediately notes the similarity between this case and the reported cases of analgesia occurring clinically with jaundice.

Again, for purposes of contrast, the mixture of bile salt and bilirubin was given to a patient who had previously received bilirubin alone without beneficial effect on the arthritis. The first infusion of bilirubin and bile salt, in a ratio of 10 mg. to 40 mg., respectively, per kilogram, was followed within eight hours by relief of pain. The patient stated the

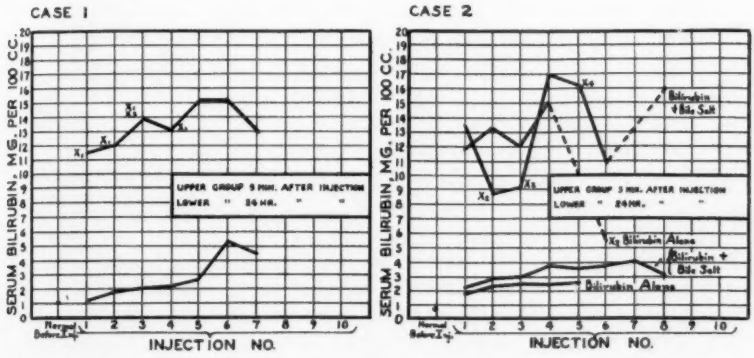


Chart 2.—Case 1 shows the clearance of bilirubin alone and the effect of adding bile salt. The dose was 10 mg. of bilirubin and 40 mg. of bile salt per kilogram, X_1 indicates that bile salt was not used in the injection. X_3 indicates a dose of 15 mg. of bilirubin per kilogram. Case 2 shows the clearance of bilirubin after intravenous injections of bilirubin alone and of bilirubin and bile salt (same patient). X_2 indicates a dose of 5 mg. and X_4, a dose of 20 mg. of bilirubin per kilogram.

next day, "I stepped out of bed this morning, and my feet and hands felt as thought I never had had arthritis." The scleras were icteric. The swelling had subsided somewhat, and none of the involved joints were painful. The serum bilirubin level at twenty-four hours was 2.4 mg. per hundred cubic centimeters (chart 2, case 2). A second and a third infusion were given, only 5 mg. of bilirubin and 40 mg. of bile salt per kilogram being used. After these two infusions there was some pain in the joints, and, as he said, "the results were not nearly as good as on the first day." For the fourth injection there was a 10 to 40 mg. per kilo-

gram ratio of bilirubin to bile salt, and this resulted in complete analgesia. The fifth injection contained 20 mg. of bilirubin and 40 mg. of bile salt. The sixth, seventh and final injections employed 10 mg. of bilirubin and 40 mg. of bile salt per kilogram. The patient stated that the joints were better than they had been for a year. The swelling had diminished, pain had disappeared and he was definitely icteric. The serum bilirubin level was 3.12 mg. per hundred cubic centimeters. This remission lasted three weeks, at which time the pain and swelling returned as before the administration. This case indicates some correlation between the serum bilirubin level and the analgesia, i. e., when 10 mg. of bilirubin (and bile salt) per kilogram was given, it produced a theoretical rise in the serum bilirubin level of 14 mg. per hundred cubic centimeters, with resulting analgesia, but 5 mg. of bilirubin per kilogram, producing a theoretical rise in the serum bilirubin level of 7 mg. per hundred cubic centimeters, did not result in analgesia. This observation also indicated that since there was apparently an analgesic serum bilirubin level, each dose should reach this or a slightly higher level. Hence, in the succeeding cases this dosage was employed unless for experimental or other reasons it was altered.

The combination of bilirubin and bile salt was then given to eight patients with chronic atrophic arthritis. A summary of the data for these patients is tabulated in table 3. The two cases just cited are included in the summary.

Briefly, the observations are as follows: Of ten patients, three received seven; two, eight; three, nine; one, ten, and one, eleven daily infusions of bilirubin and bile salt. The first observable icterus in the eyes was noted after the first to the fourth injection. This became generalized after two to eight injections. However, varying degrees of intensity were noted; as a general rule the icterus became progressively more marked with each succeeding injection. The observable jaundice disappeared from fourteen to twenty-three days after the last administration. A diminution of the swelling was noted after one to nine infusions. Analgesia was noted after one to seven injections and persisted for varying intervals, the shortest period being twelve days. The longest period cannot be determined as five patients have had no return of pain up to the time of writing (elapsed intervals of five, five and one-half, two, one and one month, respectively).

The serum bilirubin levels before the administration and at five minute and twenty-four hour intervals after each injection are shown in table 4 and charts 3 to 5 (the five minute sample of blood was taken from a contralateral vein; the twenty-four hour sample was taken from a vein just previous to the injection of bilirubin and bile salt into that vein). The clearance of bilirubin from the blood stream was rapid after

TABLE 3.—*Summary of Observations on Ten Patients with Chronic Atrophic Arthritis Receiving Bilirubin and Bile Salt in Repeated Intravenous Injections*

Case No.	Duration of Arthritis, Years	Severity	Total Number of Infusions of Bilirubin and Bile Salt Given	Icterus: Onset After Infusion, Number: Eyes	Icterus: Onset After Infusion, Number: Skin	Icterus: Duration After Final Infusion, Days	Analgesia: Onset After Injection Number	Swelling: Onset After Injection Number	Effect and Duration
1	4.0	Marked	7	3	5	18	1	1	Analgesia; diminished swelling continuing to present (5 months)
2	3.5	Moderate	7	..	5	18	1	1	Analgesia; diminished swelling for 21 days
4	2.5	Marked	7	3	6	21	7	7	Analgesia; diminished swelling continuing to present (5½ months)
5	6.0	Marked	8	1	6	18	4	1	Analgesia; diminished swelling for 12 days
6	2.0	Moderate	9	2	2	21	4	4	Analgesia; diminished swelling for 21 days
7	6.5	Marked	9	4	8	23	4	9	Analgesia; diminished swelling continuing to present (2 months)
8	3.0	Marked	9	2	5	14	5	..	Analgesia for 15 days
9	7.0	Marked	8	2	4	21	5	6	Analgesia; diminished swelling for 18 days
10	11.0*	Moderate	10	2	6	20	2	2	Analgesia; diminished swelling continuing to present (1 month)
11	1.0	Moderate	11	2	7	22	4	2	Analgesia; diminished swelling continuing to present (1 month)

* Still's disease had been relatively quiescent for three years, with an exacerbation of six weeks' duration.

TABLE 4.—*Serum Bilirubin Values* After Repeated Intravenous Injections of Bilirubin and Bile Salts*

Case No.	Normal Value	Injection No. 1		Injection No. 2		Injection No. 3		Injection No. 4		Injection No. 5		Injection No. 6		Injection No. 7		Injection No. 8		Injection No. 9		Injection No. 10		Injection No. 11	
		5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval	5 Min. Interval	24 Hr. Interval
1	1.20	11.60†	1.02	12.00†	1.70	14.00‡	2.10	13.80†	2.09	15.30†	2.80	15.39	5.39	13.70	4.50	.....	....	.....	....	.....	....	.....	....
2	0.67	13.40	2.14	8.90§	2.90	9.40§	3.00	17.00	3.90	16.29‖	3.70	10.75	3.90	.....	4.10	16.00	3.12	.....	....	.....	....	.....	....
4	1.28	13.90	2.10	14.80	2.95	12.40	3.80	13.70	2.91	16.90	3.40	12.20	4.10	17.90	4.50	.....	....	.....	....	.....	....	.....	....
5	1.84	12.90	1.01	11.91	2.90	13.90	3.50	12.80	2.41	16.30‖	3.40	.....	3.50	.....	3.96	.....	3.57	.....	....	.....	....	.....	....
6	1.77	26.92‖	3.62	12.47	2.76	11.05	....	11.42	2.75	13.25	3.37	12.72	3.40	12.72	4.95	35.47‖	5.03	16.04	3.79	.....	....	.....	....
7	1.35	13.48	3.34	10.45	3.47	10.53	....	11.82	2.85	11.82	2.57	12.96	3.34	12.96	4.43	32.09‖	3.71	14.02	3.30	.....	....	.....	....
8	1.63	5.76	1.31	14.40	3.15	12.72	3.34	13.75	3.40	18.72	3.96	16.44	4.16	19.82	4.97	21.06	4.05	21.03	....	.....	....	.....	....
9	1.77	12.47	2.98	14.10	3.83	17.28	3.55	19.26	3.75	17.28	3.87	21.74	4.74	17.73	3.86	19.25	....	.....	....	.....	....	.....	....
10	0.94	14.34	1.41	16.85	2.90	.....	4.57	.....	1.83	16.30	3.96	17.90	3.57	18.87¶	3.20	¶	4.04	¶	4.38	2.26¶	5.01	.....	....
11	1.72	14.21	1.50	.....	2.70	16.30	3.63	10.21	1.75	10.78	3.53	12.67	3.08	¶	3.15	18.20¶	4.99	16.00¶	3.77	12.00¶	4.77	21.50¶	5.10

* The Ernst-Förster method was employed. The values are given in milligrams per hundred cubic centimeters.
† Bilirubin was given alone.
‡ Bilirubin was given alone; 15 mg. per kilogram.
§ The dose of bilirubin was 5 mg. per kilogram.
‖ The dose of bilirubin was 20 mg. per kilogram.
¶ The dose of bilirubin was 15 mg. per kilogram.

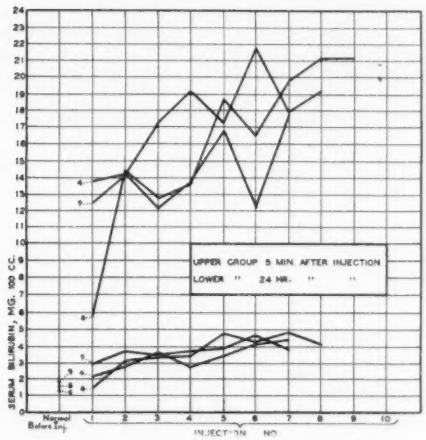
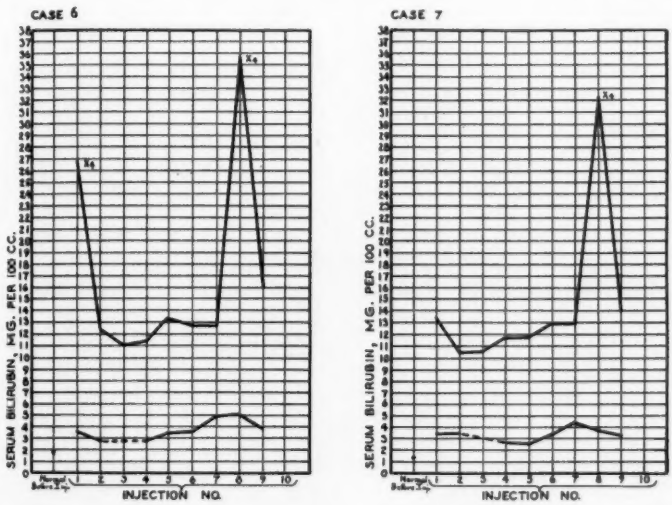


Chart 3.—The clearance of bilirubin after repeated intravenous injections of bilirubin, 10 mg. per kilogram, and bile salt, 40 mg. per kilogram.



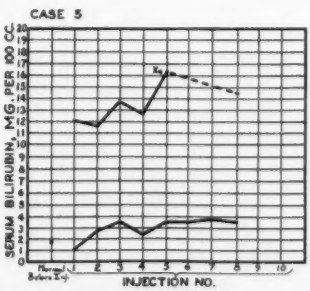


Chart 4.—The clearance of bilirubin after repeated injections of bilirubin in doses of 10 or 20 (X_4) mg. per kilogram with 40 mg of bile salt per kilogram. In each case the upper curve indicates values obtained five minutes after the injection, and the lower curve, values obtained twenty-four hours after the injection.

both single and repeated infusions of the mixture of bilirubin and bile salt. However, after the repeated administration there was a rise in the twenty-four hour levels. Despite these low levels for bilirubin in the blood at twenty-four hours, there was sufficient retention in the tissues to produce varying degrees of icterus. The serum bilirubin appeared to be of exogenous origin, since the levels for the five minute samples approximated or were lower than the theoretical levels. The obtaining of low values at five minutes may be due to the rapid clearance of bilirubin from the blood stream.[12]

Reactions occurred in some of the patients receiving bilirubin and bile salt. From a total of eighty-five infusions, fifteen reactions appeared in six patients. Four patients had no reactions. These reactions were

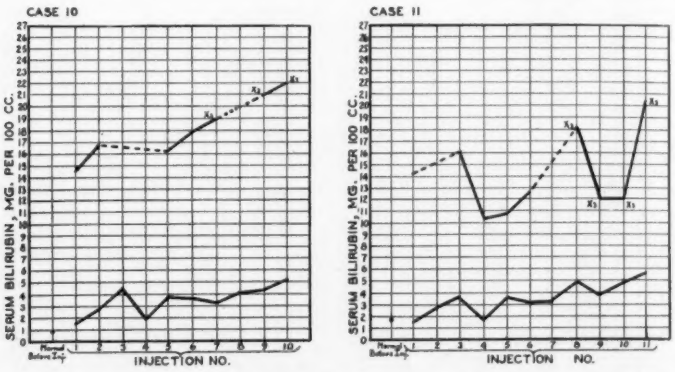


Chart 5.—The clearance of bilirubin after repeated injections of bilirubin in doses of 10 or 15 (X_3) mg. of bilirubin with 40 mg. of bile salt per kilogram. In each case the upper curve indicates values obtained five minutes after the injection, and the lower curve, values obtained twenty-four hours after the injection.

local or general. Local reactions occurred when the same vein was used for consecutive injections. General reactions were immediate or delayed. The immediate reactions observed were flushing of the face, tachycardia and subjective sensations of fulness in the head and headache. Delayed reactions occurred one to two hours after injection and consisted of nausea, vomiting, chills, a temperature of 99 to 101 F. and, subjectively, a dull ache in the back or head. All general reactions were of short duration and never appeared dangerous. The only medication required was 30 drops of aromatic spirit of ammonia, which promptly relieved the immediate general reaction. Slight diuresis occurred in these patients, and loose stools were noted occasionally.

12. Dragstedt, C. A.: Personal communication to the authors.

There appeared to be no toxic effects other than the reactions. Tests of renal function (phenolsulfonphthalein) and tests of concentration and dilution (Mosenthal), as well as daily urinary examination, exhibited no evidence of renal damage before, during or after the administration. No evidence of hepatic damage (as judged by the bromsulphalein hepatic function test [13]) was revealed. In addition, the clearance of bilirubin from the blood was indicative of the functional capacity of the liver.[14] Additional laboratory data were obtained from complete blood counts, agglutination titers of the serum to hemolytic and green-producing streptococci, sedimentation rates (Westergren) and cultures from foci of infections. These studies were made immediately before and after the series of tests. Except for the change in sedimentation rate and the appearance of bile pigments in the urine, no noteworthy changes occurred (table 5).

Since neither bilirubin nor bile salt alone has an analgesic effect, the mechanism of their combined action is somewhat problematic. The first question that presented itself was: Is there a higher and more persistent hyperbilirubinemia when bilirubin and bile salt are used together than when bilirubin is used alone? The observations on the patients and on rabbits indicate that there is a slightly higher and more persistent hyperbilirubinemia when the two are used together than when bilirubin is used alone. However, the differences are not striking, and the clinical relief of symptoms has not been sufficiently parallel to the degree of bilirubinemia to permit one to draw any conclusions.

When we first employed this solution, we encountered several difficulties, but eventually we arrived at the following technic of preparation, which has been successful in our hands:

Sufficient tenth-normal sodium carbonate for complete solution of the bilirubin (we have used 20 to 30 cc. to 0.1 Gm.) is brought to the point of boiling. The bilirubin is added, and the mixture is allowed to stand for one hour, with occasional gentle agitation. The solution is then passed through a Seitz filter. A sterile solution of bile salt is added to the filtrate. The solution is protected from the light at all times. This final solution is sterile and is administered intravenously by the gravity method directly after preparation. No difficulties have been encountered when we have prepared the solution in this manner.

CONCLUSIONS

Confirmatory of the reports of others, it was found that the administration of bile salt was without beneficial effect on the symptoms of chronic atrophic arthritis. Bilirubin alone employed similarly gave no

13. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, Philadelphia, W. B. Saunders Company, 1932, pp. 94 and 100.

14. von Bergmann.[8a] Eilbott.[8b] Harrop and Barron.[8c]

TABLE 5.—*Summary of Laboratory Data Determined Immediately Before and After a Series of Intravenous Injections of Bilirubin and Bile Salt*

	Blood							Kidney					Liver:
	Erythrocytes, Millions per Cu. Mm.	Hemoglobin, per Cent	Total Leukocytes	Sedimentation Rate, Mm. per Hr.	Agglutination Titers		Focal Infection	Urine Analysis	Phenolsulfonphthalein Test, %		Concentration and Dilution Specific Gravity		Bromsulphalein Test, at 30 Min.
									1 Hr.	2 Hr.			
Case 1: Before	4.6	95	6,250	75	1:80	1:100	—	Occult red blood	..		.....		.....
After	4.6	97	5,650	53	1:80	1:160	—	Trace of bile	..	..	.....		.....
Case 2: Before	4.61	91	7,000	71	Neg.	Neg.	—	Trace of albumin	..	..	.....		.....
After	4.5	88	8,000	85	Neg.	Neg.	—	Trace of albumin and bile	..	..	.....		.....
Case 4: Before	4.61	91	7,000	91	Neg.	Neg.	—	Normal	..	..	.....		No retention
After	4.6	97	7,100	25	Neg.	Neg.	—	Trace of bile	..	..	.....		.....
Case 5: Before	4.85	97	9,800	105	1:640	1:1,280	—	Normal	..	..	.....		.....
After	4.62	95	7,700	113	1:640	1:1,280	—	Trace of bile	..	..	.....		.....
Case 6: Before	4.81	97	7,200	105	1:320	1:640	—	Normal	45	75	.....		.....
After	4.72	97	6,250	45	1:320	1:640	—	Trace of bile	45	80	.....		No retention
Case 7: Before	4.98	97	7,400	31	Neg.	Neg.	—	Normal	..	..	.....		.....
After	5.23	85	7,430	42	Neg.	Neg.	—	.....	..	..	.....		.....
Case 8: Before	4.91	97	8,700	61	1:640	1:1,280	—	Normal	..	..	.....		.....
After	4.87	95	7,950	72	1:640	1:1,280	—	Trace of bile	..	..	.....		.....
Case 9: Before	4.58	88	7,000	63	1:320	1:320	—	Normal	..	..	.....		.....
After	4.05	80	7,430	101	1:320	1:320	—	Trace of bile	..	..	.....		.....
Case 10: Before	3.92	80	7,450	60	Neg.	Neg.	—	Normal	45	80	1.007	1.028	No retention
After	3.9	80	7.450	15	Neg.	Neg.	—	Trace of bile	50	75	1.008	1.028	.....
Case 11: Before	4.51	91	8,000	62	1:1,280	1:2,560	—	Normal	50	75	1.011	1.018	No retention
After	4.52	97	6,400	42	1:1,280	1:2,560	—	Trace of bile	40	70	1.017	1.024	.....

beneficial effects. However, the combination of bilirubin and bile salt had an ameliorating effect on the symptoms of atrophic arthritis.

The mechanism of this action is not obvious, but it seems clear from these studies that one can produce artificial jaundice which apparently duplicates the effect observed by various workers when clinical jaundice intervenes in cases of atrophic arthritis.

DISCUSSION OF PAPERS BY HENCH AND BY THOMPSON AND WYATT

DR. NATHAN SIDEL, Boston: These papers have been interesting to me because of the report which Dr. Abrams and I made on jaundice in arthritis, mention of which Dr. Hench was kind enough to include in his paper. Since the publication of our report in 1934 I have seen four other patients who showed the analgesic effect of jaundice on their arthritic pain. Two of these patients had obstructive jaundice due to carcinoma of the head of the pancreas, and the articular condition was osteo-arthritis, but there was only slight improvement. The other two patients presented rheumatoid arthritis, and with the onset of catarrhal jaundice the articular pain was markedly alleviated. It would be superfluous for me to state how dramatic the improvement is in such cases, since this has been emphasized by Dr. Hench and Dr. Thompson.

My first experience with bile salt therapy in arthritis was the giving of bile salts by mouth to the first patient in our series after his jaundice cleared. This was in 1933, and whereas the patient previously had to take 8 to 10 tablets of acetylsalicylic acid daily for relief, he felt better with the bile salts and has continued this program ever since. However, this therapy was not successful in the other cases. In 1934 I tried decholin sodium intravenously with ten arthritic patients, but there was no relief. This is consistent with the conclusion drawn from work of Dr. Thompson, that decholin sodium by itself was of no value.

I hope that commercial houses will not exploit bile salts for arthritis in view of the "jaundice analgesia." I look on jaundice as a temporary palliative but not as a cure for arthritis. Is it possible that there is a certain hepatic substance, call it an x substance, that may be helpful when the patient with arthritis takes cinchophen without obtaining toxic effects but that is excreted in excess if jaundice occurs, thus giving marked relief of the arthritis?

WILLIAM B. RAWLS, New York: During the past five years my colleagues and I have been studying the hepatic function of patients with rheumatoid arthritis. Dr. Hench's report that was published in July 1933, in which he pointed out the relief of arthritic pain noted during jaundice, suggested to us that arthritis might be related to hepatic dysfunction. Although one of our patients had had relief from pain during jaundice, we had not considered a possible relation until Dr. Hench's first report appeared.

In another investigation, which included the giving of cinchophen as a clinical test to determine the reliability of cutaneous tests with cinchophen, urticaria developed in nine of the patients. In five of them there was almost complete cessation of pain, lasting for ten days in one case to six months in another. This occurred in cases in which urticaria was severe and lasted for more than five days. As a rule when urticaria was mild, either there was no relief from pain, or the relief was only temporary.

Determinations were made of the galactose tolerance, hippuric acid excretion, azorubin S excretion, bilirubin excretion, icterus index, van den Bergh reaction,

cholesterol ester content, total cholesterol content and albumin-globulin ratio in most cases, sometimes before and after the administration of cinchophen. When there was relief from arthritic symptoms, the icterus index, the bilirubin content of the blood and the proportion of cholesterol esters to total cholesterol were increased.

Cinchophen toxicity occurred in forty-eight patients, including nine with urticaria. For fifteen of them the icterus index was determined before cinchophen was administered and again after cinchophen toxicity developed. It was increased 3 points in six cases and from 5 to 7 points in four others. If the icterus index remained below 10, there was no relief from symptoms, or the relief was only slight and temporary. If the index was above 10, symptomatic relief was usually more marked and more lasting. Those patients with an icterus index above 10 were considered subicteric. Hench reported one case in his first series and four cases in the present series in which relief was obtained apparently during the subicteric stage. We decided to test the accuracy of icterus index determinations. Repeated readings for a number of specimens indicated a mean technical error of 0.7. The icterus index showed a mean variation of 1.8 from day to day when taken under similar conditions. This indicated that variations of 2 or more points, such as those just mentioned, are significant.

In one case in which mild jaundice developed, lasting for two weeks, there was almost complete cessation of symptoms, but they returned ten days after the disappearance of jaundice. In two other cases of mild jaundice there was complete cessation of symptoms, lasting for about one month. In two instances the arthritic symptoms were worse even though the icterus index was increased to 10 and 12, respectively. Our failure to obtain cessation of symptoms for as long as was obtained by Drs. Hench and Thompson was probably due to the milder degree of jaundice. As Dr. Hench has pointed out, it seems to be a quantitative rather than a qualitative action.

In a number of cases there was a definite decrease in the ratio of cholesterol esters to total cholesterol after cinchophen toxicity developed. In one instance the esters were 64 per cent of the total cholesterol content before the administration of cinchophen and 40 per cent after symptoms of toxicity developed. The icterus index increased from 5.4 to 8.7. There was relief of symptoms for ten days.

In view of the possibility that increased values for serum bilirubin might be a factor in these cases, a number of patients were given intravenous injections of bilirubin, but without appreciable effect on the articular symptoms. Since hearing Dr. Thompson's paper, I am convinced that this was due to insufficient dosage, because our dose never exceeded 3 mg. per kilogram of body weight. This dose gives only a slight increase in the serum bilirubin content after four hours. Our experience with bilirubin has been rather limited, owing to the high cost of the drug. Further study is needed to determine whether an increase in the bilirubin content is responsible for the relief of pain in these cases.

We have also used the sodium salt of dehydrocholic acid (decholin sodium) in a large number of cases. Ten cubic centimeters of 20 per cent solution was given intravenously two or three times each week for four to six weeks or until eight or ten injections had been given. Although improvement seemed to occur in some cases, this drug should be used only for hepatic dysfunction and not as a treatment for arthritis. Its action is probably due to the increased production of bile, which relieves some of the toxicity present.

These observations suggest that the relation between jaundice and the relief of arthritic pain should receive further study.

DR. H. M. MARGOLIS, Pittsburgh: The observations of Dr. Hench and of Drs. Thompson and Wyatt are most interesting, and since they are in line with certain preliminary studies that my colleagues and I have been carrying out in Pittsburgh, I should like to relate briefly our experience.

In view of the fact that the occurrence of a significant degree of jaundice, from any cause, frequently inactivates completely an arthritic process for the duration of the icterus, we studied the therapeutic effect of certain components of the icteric state in cases of active rheumatoid arthritis. Because it was most easily available, we studied first the effect of the sodium salt of dehydrocholic acid (decholin sodium), a salt of one of the bile acids, which we injected intravenously daily over a period of a week. We employed this procedure for several patients with rheumatoid arthritis in whom the chief disability was caused by pain, periarticular swelling, stiffness and soreness. Although in one case the effect during the first few days seemed encouraging, it was soon evident that this improvement was merely coincidental, for the subsequent experience was different and I found no appreciable benefit from the administration of the bile salts. The results were so clearcut that further therapeutic trial of bile salts in arthritis was not attempted.

In view of the possibility that the relation of jaundice to improvement in the arthritic state may depend on some product of hepatic degeneration, we studied the effect of the intravenous and intramuscular injection of autolyzed liver, which was supplied me by Dr. W. S. McEllroy, of the University of Pittsburgh. This preparation, which Dr. McEllroy has employed in the treatment of pernicious anemia, is made by adding a dilute solution of hydrochloric acid to minced beef liver to which small amounts of chloroform are added as a preservative, the mixture being shaken, placed in an incubator and allowed to undergo autolysis for an average of ten days, during which time it is shaken daily. At the end of ten days the undigested material is removed by filtration. Some of this filtrate was used after the reaction to neutrality had been adjusted and after sterilization by Berkefeld filtration. Since this preparation contains various products of protein degradation which are likely to produce severe reactions, the material was diluted in physiologic solution of sodium chloride or 5 per cent solution of dextrose. The intravenous injection of such a solution of autolyzed liver in two cases of atrophic arthritis produced distinct exacerbation of the symptoms of pain, stiffness and soreness. During the course of a series of injections, improvement did not occur, but rather an exacerbation of all the symptoms. The adverse effect was so clearly evident that this procedure also was discarded.

During all this time I felt that the relief of arthritic pain afforded by the icteric state is probably effected not by any single chemical factor but by some combination of factors inherent in the jaundiced state. I am glad to find that the observations of Dr. Thompson and Dr. Wyatt confirm this view to a large extent. While we did not attempt any study with pure bilirubin or a combination of bilirubin and bile salts, as Dr. Thompson did, we played with the idea that the perfect experiment would be the administration to such arthritic patients of whole bile, if some way could be devised to eliminate the known high toxicity of bile. To study the toxicity of whole bile, Dr. McEllroy and I injected into a dog a preparation of ox bile intravenously. Toxic manifestations resulted immediately, with nausea and vomiting and, later, evidence of cerebral confusion and motor incoordination, from which the dog recovered, however, within twenty-four hours. This reaction was so marked that we did not feel justified in repeating the experiment clinically, particularly since it was evident that such large amounts of whole bile would be required that it would be distinctly hazardous. That is as far as our experiments have gone, but we are still intensely interested in the problem

of devising some means of duplicating that biologic state which, in spontaneous jaundice, produces these frequently remarkable clinical remissions in the arthritic patient. The present report by Dr. Thompson and Dr. Wyatt points the way to further study along this line—studies which may give some cue to certain biochemical factors capable of influencing the arthritic state favorably.

I can testify to one other point brought out by Dr. Hench—that the effect of jaundice is somehow selective for rheumatoid arthritis and is apparently ineffective in gout. This was observed in one of my gouty patients recently, in whom an acute exacerbation of gouty arthritis was preceded by acute hepatitis with jaundice. The gouty arthritis in this case appeared, in fact, during the course of the icterus.

Dr. Philip S. Hench, Rochester, Minn.: When Dr. Thompson first wrote me last December about his studies, I was greatly interested. Many of the difficulties I have encountered in my study of the phenomenon would be eradicated were one able to produce at will nontoxic jaundice of standard pattern, relatively uniform in type, duration and intensity. In my cases of spontaneous jaundice there were many variables to contend with: the variable duration, extent and intensity of the rheumatism, and the different types, intensity and duration of the jaundice. These differences taught me something about the potency of the reaction and the effectiveness of different types of jaundice but made it difficult to form other than tentative conclusions on certain points. With one group of variables under control, it should be easier to isolate the agent responsible for the phenomenon and the mechanism whereby it works.

It will be noted that I am discussing the procedure of Drs. Thompson and Wyatt not as a therapeutic measure, not as an end in itself, but as a means to an end. Dr. Thompson and I agree on that point. I hope that no one will conclude that jaundice cures rheumatism and that this type of artificial jaundice is the long-sought cure for the disease. To adopt the term therapeutic jaundice at this stage would be forcing a bud to premature flowering. It would court the disappointment of patients and obscure a better goal—a form of treatment simpler, more rational and probably much more effective. By adopting this point of view, however, I am not belittling Dr. Thompson's work in the least. I believe that he has made a most important contribution to the problem, and if his procedure can be readily repeated with equally successful results, he has taken us a long step toward the solution of the problem. First, he has demonstrated a method for successfully producing apparently harmless "jaundice," or hyperbilirubinemia, which should be of value in studying a number of physiologic and clinical problems other than the one under discussion.

Dr. Thompson's study leads to the conclusion that there is some potent reaction between bilirubin and bile salts which is responsible for the phenomenon, and it may be so. As noted in my paper, I have been unwilling to stress the importance of bilirubin for various reasons. Among other phenomena, pregnancy, which seems to have little or nothing to do with bilirubin, often provokes a similarly effective if less dramatic remission in atrophic arthritis. A colleague and I are about to publish details of a study made on about twenty pregnant arthritic women, almost all of whom noted marked amelioration or complete disappearance of symptoms of arthritis when they became pregnant. If this represents a chemical "control," I wonder if nature in the last analysis has more than one way of controlling the arthritic process. There should be some common denominator between the two reactions, and, offhand, bilirubin seems to be excluded. If my four patients who told me their relief came before jaundice was visible were correct, either bilirubin is not responsible, or small amounts are

effective—an idea contradicted by certain data. It is of course possible that the four patients had unrecognized jaundice, but if they did not have, or even if they had, subclinical jaundice, it suggests that significant excesses of bilirubin are not required.

The study implies also that bile salts are in part responsible for the relief. Certain claims have been made in Europe for bile salt therapy in arthritis. But if a significant increase of bile salts is necessary for the reaction, it seems that I should not have seen the phenomenon continue with jaundice in the presence of severe hepatitis when presumably there is a reduction, not an increase, in circulating bile salts. The observation that two patients did not obtain relief after four doses of bilirubin but did obtain relief when bile salts was added to the fifth dose of bilirubin is most interesting but needs further investigation. One might argue that a cumulating hyperbilirubinemia was developing that was about to be effective without bile salts. However, Dr. Thompson has made no premature deductions as to what the agent may be. He has merely described a method for use in the elucidation of the problem, and, as he has said, much further work is needed to determine how the reaction induces a remission. At least three substances are injected: large amounts of bilirubin, large amounts of sodium carbonate and fairly large amounts of bile salts. The role of each must be fully established.

About two months ago, when his results were consistent enough and the details of his technic were worked out, Dr. Thompson gave me his preliminary plan in order that I might have some experience with it to bring to this discussion. He has described his technic in five sentences, and the method sounds simple enough. But to me it is not as simple as it sounds. Dr. Thompson warned me that we might have difficulties at first, and we have had them. First, the strong alkali continues to irritate or cause thrombosis in our patients' veins, so that the matter of giving eight to twelve consecutive injections to the average thin, hyposthenic arthritic patient becomes a problem. According to Dr. Thompson, the solution must be made fresh daily (a matter of about two hours), must be administered promptly and must be kept away from sunlight at all times to prevent oxidation of bilirubin. It remains to be proved how necessary some of these precautions are and whether significant oxidation can occur in the ordinary laboratory lighted mainly by electricity and with the solutions in glass containers which are considered essentially impervious to light rays capable of producing much chemical change. Will not heating the solution (unless it is under a layer of nitrogen) produce more oxidation than sunlight or electric light? But these technical difficulties will be solved eventually.

In the eight weeks at my disposal I have been able to treat only six patients, each with active atrophic arthritis. One became jaundiced, and the serum bilirubin content showed several peaks between 15 and 29 mg. But although he received seventeen injections (some of them in doses of 1 Gm.), he noted no relief. One patient received twelve injections and became definitely jaundiced, the serum bilirubin content showed several peaks between 10 and 26 mg., and he noted partial relief only—perhaps 50 per cent for a few days. Unfortunately, venous thrombosis developed, and we could not give him more injections. In an attempt to avoid these reactions we buffered the solution, bringing it almost to neutrality, but two patients treated with such a solution had excretion curves totally different from the others. Neutralization made the solution impotent to produce cumulative hyperbilirubinemia after six injections. Our last two patients have received daily doses of 1 Gm. of bilirubin and 4 Gm. of decholin sodium to produce saturation as fast as possible. They have received eleven and thirteen daily injections, respec-

tively, up to the present; both are decidedly jaundiced with the serum bilirubin content showing peaks of 25 and 34 mg. and low points of 7.9 and 12.5 mg., yet neither has yet noted any analgesia. (After a few more injections both patients experienced considerable relief of pain.) One who had hydrops and fever has noted no change in these features either. Thus, ironically, I am so far unable to corroborate Dr. Thompson's findings, which I should so like to do, since they amply corroborate and extend my own observations on spontaneous jaundice.

Now what is wrong? I do not believe it is Dr. Thompson's fault. I believe he is obtaining the results that he has reported. Realizing that a preliminary experience of only eight weeks gives one little right to draw conclusions, I merely wish to state that there must be differences between his technic and mine which, though they appear to be minor, are of greater importance than we have realized. In going over my technic carefully with him I found two or three little differences which may be important; for example, we added the bile salts before, rather than after, filtration. Nevertheless, one must conclude that the procedure is an empiric, not a rationalized, one. It is not simply a question of dissolving a certain amount of bilirubin in any alkali, adding bile salts and administering the mixture. The hypothetic x substance may be in or may be engendered by his solution but not by ours, although we have been using the same preparation of bilirubin and bile salts (decholin sodium). Is the x substance really dependent on his bilirubin-decholin sodium mixture, or is it dependent on something else in his solution? Commercial solutions of bilirubin are not really pure. There are impurities in the bilirubin that both of us have been using. Pure bilirubin contains 8.95 per cent nitrogen; commercial bilirubin contains 7.2 to 8.3 per cent nitrogen. Whether this is a factor and whether oxidation is to be avoided or actually welcomed, these and other details are to be worked out. I am not discouraged by these preliminary differences in results. Indeed, they may help in solving the problem. In the meantime, they emphasize what was said before: Dr. Thompson is not presenting "therapeutic jaundice," but when his method is standardized and rationalized, it may help in realizing to the fullest the therapeutic implications implied in the phenomenon which I have observed occurring with spontaneous jaundice.

DR. HARRY E. THOMPSON, Tucson, Ariz.: Dr. Sidel's results with the administration of bile salt alone are similar to ours. Dr. Rawls has used bilirubin alone, but he has given it in doses of only 3 mg. per kilogram, and he has not employed it in conjunction with bile salt.

In regard to Dr. Hench's discussion, when we went over this procedure previous to the meeting it was evident that he had not followed the exact procedure which I gave him a few months ago. He had made several changes. Both he and I agree that although these are minor changes, they are perhaps of major importance. This, I am sure, accounts for differences in our results. In an effort to confirm our work he has mentioned that one patient was 50 per cent improved. This indicates to me that despite the changes made in the procedure, he was sufficiently close at that time to approximate our results in part. I think that closer adherence to the procedure—both as to the preparation and as to the administration—will result in comparable clinical results. That nontoxic jaundice can be produced is apparent, as Dr. Hench has confirmed our work with relation to its production. Dr. Hench is to be congratulated for his keen observation that jaundice intervening clinically may produce a remission in atrophic arthritis.

I, too, am of the opinion that both bilirubin and bile salt should be kept free from exploration. To exploit such substances, promising as they appear, is undesirable and unwarranted at this time.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S. McCANN, M.D.
ROCHESTER, N. Y.

The period covered by this review is marked chiefly by notable achievements in the study of renal function and of the pathogenesis of renal hypertension. These achievements consist in the bringing to fruition of investigations which have covered a considerable time. These investigations have been chiefly in the field of physiology and of experimental pathology. The fruit of the achievements consists in providing the clinical investigator with sound tools with which to proceed. Many other valuable investigations have been reported, the ultimate significance of which is not so apparent. Attention will first be given to those fields in which the pattern of the mosaic may be most clearly discerned.

STUDIES OF RENAL FUNCTION

The modern theory of renal function, based on the conception of glomerular filtration and tubular resorption, appears each year to be more firmly established. For a long time it has been apparent that there is need of quantitative methods for the separate measurement of these two phases of the secretion of urine. Progress along this line began with the measurement of the urea clearance by Van Slyke and his co-workers. The conception of the "clearance" was applied to other substances which are either normally present in the plasma or which may be made to appear in it. The proposal of Rehberg and Holten that creatinine clearance could be used as a measure of glomerular filtration has been a fruitful one, in that it has been subjected to critical investigation in the course of which comparisons have been made with other substances, such as sucrose, phenolsulfonphthalein (phenol red), inulin and several other substances. A good review of the extensive investigations along these lines is to be found in the recent monograph by Homer Smith [1] entitled "The Physiology of the Kidney."

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

1. Smith, Homer W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.

In order to secure a perfect measure of glomerular filtration it is necessary to measure the clearance of some substance which is not reabsorbed in the tubules. Richards, Westfall and Bott [2] have completed conclusive experiments on the use of creatinine and inulin for this purpose. In previous experiments of Hendrix, Westfall and Richards, inulin, which has a molecular weight of about 5,000, was found in the glomerular filtrate of Necturi in the same concentration as in the plasma. Richards takes the inulin clearance as the equivalent of glomerular filtration. Over a wide range of urinary flow and of concentrations of plasma and urine the kidneys of normal dogs were found to excrete both inulin and creatinine by glomerular filtration. Neither substance was found to be reabsorbed from the tubules either actively or by diffusion. These authors, however, studied a dog which had previously been poisoned with uranium. In this case insulin was discovered to be excreted consistently at a faster rate than was creatinine. This was taken to indicate that the normal impermeability of the tubules to back diffusion of creatinine had been impaired so that 13 per cent was returned to the blood. From these observations it appears that inulin provides a better measure of glomerular filtration than creatinine under some conditions of tubular injury. Other types of tubular injury will need to be studied before one can be certain that similar back diffusion of inulin may not occur.

Goldring and Smith [3] have investigated the phenolsulfonphthalein clearance at low plasma levels as a measure of tubular activity, since at these low levels most of the dye is bound by the plasma colloids. In their observations glomerular filtration was measured by the inulin clearance. They have attempted to draw conclusions as to the states of function in glomeruli and tubules by changes observed in the phenolsulfonphthalein : inulin clearance ratios. They indicate, however, that changes may occur as a result of changes in renal blood flow.

It appears to me, however, that another phase of phenolsulfonphthalein clearance must be considered, as a result of some investigations of Ehrström [4] concerning the disappearance of congo red from the plasma in amyloid disease. Ehrström found that in certain conditions the binding power of the plasma proteins for congo red is impaired. If this is true there might also be conditions in which plasma proteins would bind phenolsulfonphthalein less securely. This would alter the

2. Richards, A. N.; Westfall, B. B., and Bott, P. A.: Inulin and Creatinine Clearances in Dogs, with Notes on Some Late Effects of Uranium Poisoning, J. Biol. Chem. **116**:749, 1936.

3. Goldring, W., and Smith, H. W.: Differentiation of Glomerular and Tubular Function in Glomerulo-Nephritis, Proc. Soc. Exper. Biol. & Med. **37**:180, 1937.

4. Ehrström, M. C.: Ueber veränderte physikalische Eigenschaften der Plasmaproteine bei Nephrose, Acta med. Scandinav. **90**:427, 1936.

normal relations between free and bound phenolsulfonphthalein, on which the assumptions of Goldring and Smith were based.

Winkler and Parra [5] compared the clearances of creatinine, sucrose and urea of normal and nephritic subjects. The order of magnitude of the clearances is creatinine > sucrose > urea. They vary together. For normal subjects the creatinine clearance was found to be higher immediately after ingestion of creatinine, with a tendency to decrease with time. By subjects with renal disease for whom these clearances were reduced, the same relative magnitudes were retained, and a tendency of the creatinine clearance to fall off with time was not observed.

In Copenhagen, studies of the renal function during the course of scarlet fever and scarlatinal nephritis have been made by Gram.[6] Daily measurements were made of the urea clearance and urinary sediment. For 7 patients with scarlet fever and complications other than nephritis, high clearance values were found during the first ten days. Later, during the fourth and fifth weeks, low values were usually observed. All patients excreted casts and erythrocytes at various times. In 5 the blood pressure was normal; in 2 it was elevated. The patients with scarlet fever in whom nephritis developed showed a decrease in urea clearance by the end of the first week, in contrast to those in whom nephritis did not develop and for whom low clearance values were obtained mostly in the fourth week.

In other acute infections, high rates of urea clearance have been observed at the height of the disease. In 1931 Goldring [7] observed high values in the acute stage of rheumatic fever, while low values were observed during convalescence. He [8] made similar observations in cases of lobar pneumonia. Similarly, Farr and Abernethy [9] obtained high values for young persons with lobar pneumonia, not only during the precritical stage but for a month afterward. These high rates of urea clearance were chiefly observed for persons under 40 years of age. For older subjects less elevation was found.

---

5. Winkler, A. W., and Parra, J.: The Measurement of Glomerular Filtration: Creatinine, Sucrose and Urea Clearances in Subjects Without Renal Disease, J. Clin. Investigation **16**:859, 1937; The Measurement of Glomerular Filtration: Creatinine Sucrose and Urea Clearances in Subjects with Renal Disease, ibid. **16**:869, 1937.

6. Gram, C. N. J.: Renal Function During the Course of Scarlatine and Scarlatinal Nephritis, Acta med. Scandinav. (supp.) **78**:778, 1936.

7. Goldring, W.: Studies of the Kidney in Acute Infection: II. Observations of the Urea Clearance Test in Acute Rheumatic Infection, J. Clin. Investigation **10**:345, 1931.

8. Goldring, W.: Kidney in Acute Infection: Sediment Count (Addis) in Lobar Pneumonia, J. Clin. Investigation **10**:355, 1931.

9. Farr, L. E., and Abernethy, T. J.: Renal Physiology in Lobar Pneumonia, J. Clin. Investigation **16**:421, 1937.

ADDIS SEDIMENT COUNTS IN ACUTE INFECTIONS

In pneumonia Farr and Abernethy [9] found no abnormal values for erythrocytes. The number of casts was usually increased, that of the hyaline casts especially. Granular casts were found in the cases of more severe pneumonia. Proteinuria was generally slight, rarely over 0.1 Gm. of protein being excreted daily. Abnormalities of the urinary sediment tended to disappear as the fluid balance was reestablished. No instance of nephritis was observed in their series of 28 patients. In 1931 Goldring [8] observed 2 patients who had diffuse glomerulonephritis during convalescence from pneumonia, but in general his findings agreed with those of Farr and Abernethy.

Gram [6] believes that the majority of patients with scarlet fever have latent nephritis and that they may be grouped as follows: (1) those with intermittent hematuria but normal blood pressure and urea clearance; (2) those with constant and profuse cylindruria, with either a normal or an elevated blood pressure; (3) those with chemically demonstrable hematuria, increased blood pressure and slight edema but no azotemia.

This recalls the work of Lyttle,[10] who studied 14 patients with scarlet fever, finding that all showed transient increase in the excretion of protein and formed elements in the period from eight to forty-five days after the onset. He said he believed that renal damage was so slight that only unusually careful examination would reveal it and that in the majority of cases the nephritis was aborted by a satisfactory immunologic adjustment.

In a previous review,[11] reference was made to the work of Goldring and Wykoff, who found that the excretion of formed elements and protein occurred in excess of normal in 16 cases of rheumatic fever.

Concerning the prognosis for recovery of children who have had postinfectious nephritis, there is some divergence of views. Boyle, Aldrich, Frank and Borowsky [12] followed the urinary sediment counts of 25 children for periods of one-half to eight years. With the exception of 1 girl, all showed normal counts. In this 1 case, in which occult hematuria was present, hydronephrosis was discovered.

On the other hand, Snoke [13] presents the results of a study of 154 children observed between 1920 and 1936 in the Stanford Children's

10. Lyttle, J. D.: The Addis Sediment Count in Scarlet Fever, J. Clin. Investigation **12**:95, 1933.

11. McCann, W. S.: Bright's Disease: A Review of Recent Literature, Arch. Int. Med. **55**:512 (March) 1935.

12. Boyle, H. A.; Aldrich, C. A.; Frank, A., and Borowsky, S.: The Addis Count in Children Following Clinical Recovery from Post-Infectious Nephritis, J. A. M. A. **108**:1496 (May 1) 1937.

13. Snoke, A. W.: Stages, Prognosis and Duration of Glomerular Nephritis in Childhood, Am. J. Dis. Child. **53**:673 (March) 1937.

Clinic who had glomerulonephritis. Of these, 37 per cent are now healed, 21 per cent are dead and 42 per cent still have active nephritis. Snoke feels that in practically no case can glomerulonephritis of more than two years' duration be expected to heal. He estimates the eventual mortality rate in this series of cases at 40 per cent. The persistence of latent glomerulonephritis is frequently missed unless quantitative examination of properly concentrated urine is made.

In the accompanying table are recorded the sediment counts observed by Boyle and his co-workers [12] for patients who had recovered from glomerulonephritis, compared with the various normal standards of Addis,[14] Lyttle,[15] Goldring [16] and Naeraa.[17]

Sediment Counts for Children Who Had Recovered from Nephritis Compared with Normal Standards of Various Authors *

	Status of Child	Number of Casts	Number of Erythrocytes	Number of Leukocytes and Epithelial Cells
Boyle [12]	After recovery from nephritis	0-18,611 3,401	0-114,000 19,817	0-990,000 337,000
Addis	Normal	0-4,270 1,040	0-425,500 65,750	32,400-1,835,000 322,500
Lyttle	Normal	0-12,916 1,085 ± 123	0-129,900 15,181 ± 1,400	9,000-2,822,000 322,184 ± 25,500
Goldring	Normal	0-9,200 1,300	0-1,530,000 146,000	24,000-2,430,000 540,000

* The upper figures represent the range of variation, and the lower figure represents the mean value.

PREVENTION OF GLOMERULONEPHRITIS

Peters and Cullum [18] have compared the statistics on the incidence of scarlet fever and of scarlatinal nephritis in the Ham Green Hospital, in Bristol, England, for the period from 1910 to 1936. The incidences varied, but in the period from 1930 to 1934 an especially low incidence of nephritis was noted. During this period Peters was administering thyroid and iodine to the patients during the first fortnight of the

14. Addis, T.: Clinical Classification of Bright's Disease, J. A. M. A. **85**:163 (July 18) 1925.

15. Lyttle, J. D.: Addis Count in Normal Children, J. Clin. Investigation **12**:87, 1933.

16. Goldring, W.: Clinical Application of Sediment Count (Addis), Am. J. M. Sc. **182**:105, 1931.

17. Naeraa, A.: Om Addis' urinsediment bestemmels, Hospitalstid. **77**:1444, 1934.

18. Peters, B. A., and Cullum, I. M.: A Study in Prevention, Brit. M. J. **1**:1020 (May 15) 1937.

disease. The difference in incidence was 2.3 times the standard deviation and seemed significant. However, during the following year scarlet fever was very severe, and the incidence of nephritis increased in spite of this method of treatment. Thereon, alternate patients were used as controls for a comparison of the effects of the thyroid and iodine treatment and for the evaluation of Osman's alkalinization treatment in the prevention of nephritis after scarlet fever. For Osman's method there were 124 test cases and 134 controls, with no significant differences in the incidence of albuminuria and nephritis. For the thyroid and iodine treatment there were 165 test cases and 162 controls, with no significant differences between them. It appears, therefore, that the evaluation of preventive measures in such a variable disease is better accomplished by studying alternate cases than by observation of year to year variations. It is apparent also that means of prevention of postscarlatinal nephritis, apart from the prevention of scarlet fever, are still to be found.

EXPERIMENTAL NEPHROTOXIC NEPHRITIS

In a previous review [19] mention was made of the production of nephritis by Masugi and by Smadel, who used a nephrotoxic serum. Smadel and Farr [20] report the clinical and functional studies of the experimental nephritis thus produced. Clinically it is characterized by albuminuria, cylindruria and anasarca but not by hematuria. The rapidity of its development varies with the dose of nephrotoxin, ranging from two weeks to eleven months. The milder forms progress to renal insufficiency by stages resembling those of diffuse glomerulonephritis in man. Clever methods are described for determination of the urea clearance of rats, together with the method of Moberg for measurement of the blood pressure of these small animals.

Smadel [21] describes the lesions in the kidneys of rats with nephritis. They are characterized by the early swelling of the intercapillary substance of the glomerular tuft. Thrombi were present only in those cases in which anaphylactoid reactions occurred, and these were due to other factors than pure nephrotoxin. Tubular degeneration was noted, followed later by scarring of glomeruli and tubules and by widespread vascular disease, with secondary changes in the heart and brain and elsewhere.

---

19. McCann, W. S.: Bright's Disease: A Review of Recent Literature, Arch. Int. Med. **60**:167 (July) 1937.

20. Smadel, J. E., and Farr, Lee E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum: II. Clinical and Functional Studies, J. Exper. Med. **65**:527, 1937.

21. Smadel, J. E.: Pathological Studies of the Acute and Chronic Disease, J. Exper. Med. **65**:541, 1937.

Swift and Smadel [22] report that they were able to prevent the injurious effects of the administration of nephrotoxic serum by giving a saline extract of rat kidney intravenously to rats before injection of the nephrotoxic serum. The nephrotoxic effect was not inhibited by the administration of a similar extract of rat liver, although this extract was capable of absorbing the nephrotoxin in vitro.

Farr and Smadel [23] have studied the effects of diet on the course of nephrotoxic nephritis in rats which received a single injection of nephrotoxin. These were divided into three groups and were given three types of diets which were isocaloric, as follows: (1) 5 per cent protein, 64 per cent carbohydrate and 27 per cent fat; (2) 18 per cent protein, 51 per cent carbohydrate and 27 per cent fat; (3) 40 per cent protein, 29 per cent carbohydrate and 27 per cent fat. For all three the same salt mixture and sources of vitamins were used.

In group 1, 13 of the 15 rats survived, and the evidences of nephritis had disappeared in eight and one-half months. At this point 5 of the rats were given diet 3, and in the ensuing months 3 of them showed albumin and casts in the urine, though they had normal renal function.

In every animal on diet 3 progressive nephritis developed, and all but 2 were dead of renal failure in six months.

On diet 2, 8 of the 15 were dead of renal failure in five and one-half months. Of the remainder, 6 were definitely abnormal and 1 recovered.

It is apparent from these studies that the course of experimental nephritis is markedly and adversely influenced by a high proportion of protein in the diet. It appears to me that these results should be examined in the light of what constitutes a normal diet for the rat and for man. It must not be too readily assumed that because excessive proportions of protein are harmful, normal proportions will also prove to be so. The normal diet of man, given wide and free choice, will be found to derive about 15 per cent of its calories from protein. Normal Eskimos tolerate proportions as high as 45 per cent. It may well be that excessively high proportions will be found to have an adverse effect on the course of nephritis in man. This should not be taken as an excuse for protein starvation, since clinical studies by Keutmann and McCann [24] of human beings have revealed no adverse effects from a ration of protein sufficient to permit deposition of protein to replace

22. Swift, H. F., and Smadel, J. E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum: IV. Prevention of the Injurious Effects of Nephrotoxin in Vivo by Kidney Extract, J. Exper. Med. **65**:557, 1937.

23. Farr, L. E., and Smadel, J. E.: Influence of Diet on the Course of Nephrotoxic Nephritis in Rats, Proc. Soc. Exper. Biol. & Med. **36**:472, 1937.

24. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease, J. Clin. Investigation **9**:973, 1932.

large losses through albuminuria. Keutmann and Bassett [25] present data which show that maximal synthesis of new protein may be achieved with diets which are well within the limits of a normal intake of protein and which could by no means be considered high in protein.

Bearing on this same question is a paper by Blatherwick and Medlar,[26] who produced chronic nephritis in rats by feeding diets high in protein, some containing as much as 72 to 75 per cent liver or casein. Some of their diets which consisted of 25 per cent milk protein and 12 per cent beef protein led to renal injury, but diets in which the protein was as low as 20 per cent apparently did not produce these results.

HYPERTENSION IN NEPHROTOXIC NEPHRITIS

Arnott, Kellar and Mathew [27] produced nephritis by the method of Masugi. If one kidney was denervated prior to induction of nephritis, the anatomic changes produced were identical in the two kidneys. Hypertension was observed in the animals with experimental nephritis. It was found that the development of hypertension could be prevented by denervation of the kidneys before induction of nephritis. If denervation was carried out afterward, the hypertension was terminated. These results are similar to those reported by these authors previously concerning the hypertension of oxalate nephritis.

HYPERTENSION PRODUCED BY RENAL ISCHEMIA

Goldblatt [28] has recently reviewed his own work on the production of hypertension in dogs by means of renal ischemia induced by means of metal clamps applied to the renal arteries, together with the accumulating evidence of the formation of a humoral pressor substance in the ischemic kidneys. This substance is believed to act independently of the nervous mechanism of the kidney, and in Goldblatt's opinion it is independent of the endocrine glands, with the possible exception of the adrenal cortex. He gives a tabular review of the various procedures of other investigators by means of which transient hypertension has been produced by renal injury.

---

25. Keutmann, E. H., and Bassett, S. H.: Dietary Protein in Hemorrhagic Bright's Disease: II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Protein, J. Clin. Investigation **14**:853, 1935.

26. Blatherwick, N. R., and Medlar, E. M.: Chronic Nephritis in Rats Fed High Protein Diets, Arch. Int. Med. **59**:572 (April) 1937.

27. Arnott, W. M.; Kellar, R. J., and Mathew, G. D.: Hypertension Associated with Experimental Serum Nephritis, Edinburgh M. J. **44**:205, 1937.

28. Goldblatt, H.: Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69, 1937.

Goldblatt, Gross and Hanzal [29] have found that excision of the lower four dorsal sympathetic ganglions and the thoracic portion of the splanchnic nerves on both sides does not prevent, cure or permanently lower the hypertension produced by renal ischemia.

Goldblatt [30] reports success in his efforts to produce hypertension in giant macaques by the same means (clamps on renal arteries) previously used on dogs. Transient hypertension is produced by unilateral application of a clamp; a persistent elevation of both systolic and diastolic pressures follows the bilateral application.

Child and Glenn [31] accomplished denervation of a dog's kidney by transplanting it completely to the pelvis and giving it a blood supply from the femoral vessels. Application of the clamp, with the production of ischemia, caused transient hypertension. Alpert, Alving and Grimson [32] performed total sympathectomy on a dog with sustained hypertension produced by a Goldblatt clamp. The blood pressure fell but remained above the control level. When the clamps were applied to a dog which had previously been subjected to total sympathectomy, hypertension was produced.

Wood and Cash [33] report the production of persistent hypertension in dogs by means of Goldblatt's clamps.

Harrison, Blalock, Mason and Williams [34] have obtained pressor effects from saline extracts of dog kidneys when these extracts were given to rats anesthetized with pentobarbital sodium. Extracts from normal dog kidney produced a significant rise in blood pressure, but extracts from kidneys rendered ischemic produced a greater rise. When one kidney only was rendered ischemic, its extract gave a greater pressor response than did the normal kidney from the other side.

---

29. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension: II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, J. Exper. Med. **65**:233, 1937.

30. Goldblatt, H.: Studies in Experimental Hypertension: III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, J. Exper. Med. **65**:671, 1937.

31. Child, C. C., and Glenn, F.: Experimental Hypertension in Dogs by Constricting the Artery of a Single Transplanted Kidney, Proc. Soc. Exper. Biol. & Med. **37**:217, 1937.

32. Alpert, L. K.; Alving, A. S., and Grimson, K. S.: Effect of Total Sympathectomy on Experimental Renal Hypertension in Dogs, Proc. Soc. Exper. Biol. & Med. **37**:1, 1937.

33. Wood, J. E., Jr., and Cash, J. R.: Experimental Hypertension: Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, J. Clin. Investigation **15**:543, 1936.

34. Harrison, T. R.; Blalock, A.; Mason, M. F., and Williams, J. R., Jr.: Relation of Kidneys to Blood Pressure: Effects of Extracts of Kidneys of Normal Dogs and of Dogs with Renal Hypertension on Blood Pressure of Rats, Arch. Int. Med. **60**:1058 (Dec.) 1937.

From the foregoing review it is clear that Goldblatt's findings have received ample confirmation by several workers. It seems to be well established that the hypertension produced by renal ischemia is of humoral origin and independent of the renal innervation. The pressor substance appears to arise within the ischemic kidney.

HYPERTENSION IN RELATION TO PYELONEPHRITIS

Longcope [35] describes chronic pyelonephritis of adults of hematogenous origin, usually with insidious beginnings but occasionally having as an onset acute pyonephritis. Infection with Bacillus coli is usually responsible. The slow, insidious progress over a period of years may lead ultimately to renal insufficiency, frequently but not always associated with intermittent or persistent hypertension. Hemorrhagic retinitis may occur, but arteriosclerosis is not a conspicuous feature; in fact, arteriolar sclerosis was minimal in his cases post mortem.

The recognition of the disease during life is facilitated by urinary cultures and by intravenous pyelograms, which reveal dilatation of the ureters in the absence of obstruction and peculiar deformities of the pelves and calices. In 3 of 9 fatal cases the disorder was associated with diffuse glomerulonephritis.

A good description of the pathologic anatomy of pyelonephritic contracted kidneys is given by Staemmler and Dopheide.[36] These writers describe the widening of the ureters and the distortions and irregularities of the pelves without obvious obstruction; the very irregular contraction and scarring of the renal parenchyma, which is more marked than that to be expected in hydronephrotic kidneys, and the very moderate changes in the mucosa of the pelves, ureters and bladder. Microscopically these kidneys show a chronic inflammatory process, with slowly progressing obliteration of the cortex, which completely disappears in some places and assumes a thyroid-like appearance in others. Glomeruli show adhesions; in some places there is hyalinization, and in other places there is replacement by a granulation-like tissue.

These cases recall the report of Wilson and Schloss,[37] who described the pathologic changes in the kidneys of infants with pyuria. The kidneys were the seat of an interstitial suppurative process, with foci which ranged all the way from simple clusters of mononuclear and polymorphonuclear cells near blood vessels to frank abscesses. Changes

35. Longcope, Warfield T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, Ann. Int. Med. **11**:149, 1937.

36. Staemmler, M., and Dopheide, W.: Die pyelonephritische Schrumpfniere, Virchows Arch. f. path. Anat. **277**:713, 1930.

37. Wilson, J. R., and Schloss, O. M.: Pathology of So-Called "Acute Pyelitis" in Infants, Am. J. Dis. Child. **38**:227 (Aug.) 1929.

in the pelves, ureters and bladder differed from those occurring with obstruction of the urinary tract, which have been well described recently by Helmholz.[38]

Butler [39] has recently reported 15 cases of chronic pyelonephritis in children which was associated with hypertension over a period of years before there was appreciable diminution of renal function. Six of these patients died and 9 are living. Two cases of unilateral pyelonephritis with hypertension are reported in which removal of the infected kidney relieved the hypertension. Butler points out the difficulty in many cases of trying to decide whether one is dealing with primary vascular hypertension or secondary renal hypertension. In some cases of pyelonephritic contracted kidney the arteriolar sclerosis may be like that of nephrosclerosis, and the relative effects of infection and vascular change may be difficult to evaluate. It is also to be recalled that patients with malignant hypertension frequently give a history of antecedent renal infection.

RENAL LESIONS IN TOXEMIA OF PREGNANCY

The close relation between the foregoing discussion and toxemia of pregnancy is emphasized by Zimmerman and Peters [40] in a review of 23 cases of death due to "toxemias of pregnancy." Characteristic tubular and glomerular lesions were usually present in those dying in an acute eclamptic state, but they were not noted exclusively in eclampsia. Lesions characteristic of malignant nephrosclerosis were frequently seen. It appears that a variety of infectious and vascular renal diseases may act as the predisposing cause of toxemia of pregnancy. As Zimmerman and Peters express it, "Pregnancy gives them a distinctive coloration and an explosive character."

NEPHROSES

Talbott, Coombs and Consolazio [41] describe the electrolyte balance during recovery from mercurial nephrosis, beginning on the seventh day and extending through five months, of a patient who had been anuric for six days. They observed (1) depletion of the base and

38. Helmholz, H. F.: Infection of the Renal Parenchyma from the Pelvis of the Kidney, Am. J. Dis. Child. **54**:1 (July) 1937.

39. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889, 1937.

40. Zimmerman, H. M., and Peters, J. P.: Pathology of the Pregnancy Toxemias, J. Clin. Investigation **16**:397, 1937.

41. Talbott, J. H.; Coombs, F. S., and Consolazio, W. V.: Electrolyte Balance During Recovery from Mercury Bichloride Poisoning, Arch. Int. Med. **60**:301 (Aug.) 1937.

chloride of the body, (2) increase in the content of undetermined acid, (3) retention of phosphates and nitrogenous products and (4) loss of serum protein and hemoglobin.

Kerkhof [42] discusses colloid osmotic pressure as a factor in the formation and absorption of edema fluid. Using the method of Schade, he found the normal colloidal osmotic pressure to be 21.4 ± 2.5 mm. of mercury in man and 18.5 mm. in dogs. In nephrosis and nephritis the colloid osmotic pressure is usually lower than 15 and often as low as 8 mm. At 16 mm., edema fluid either is not present or is in process of absorption. He uses solution of acacia to obtain diuresis by raising the colloid osmotic pressure. In spite of previous reports of disastrous results of giving solution of acacia, Lepore [43] recommends it. He believes that the deleterious effects can be avoided and that in selected cases it is of value. He finds doses of 30 Gm. of acacia effective and employs it in 6 per cent solution.

McMaster [44] has made a comparative study of the lymphatic vessels and the flow of lymph in the skin of subjects with cardiac or with renal edema (the latter without hypertension or heart failure). He employed intradermal injections of small amounts of a vital dye, "patent blue V," and studied the effects of posture, activity and venous obstruction on lymph flow.

In both cardiac and nephrotic edema the lymphatic vessels were patent. In cardiac edema there was stagnation of the lymph, in contrast to the nephrotic edema, in which the flow of lymph was greater than normal, even during periods of fluid equilibrium, and extraordinarily rapid during periods of diuresis.

McMaster believes that the lymphatic vessels are so dilated in cardiac edema that the valves are incompetent. He seems to have overlooked the significance of the high venous pressure in heart failure which tends to impede the return of lymph to the venous system.

Ehrström [4] reports an investigation which has an important bearing on the use of the congo red test in the nephroses, in which the dye disappears rapidly from the blood stream, particularly in amyloid disease. This disappearance of dye cannot be accounted for entirely by its appearance in the urine. When he tested the plasma of normal men by adding congo red in vitro, he found that the dye was so bound by

42. Kerkhof, A. C.: Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, Ann. Int. Med. **11**:867, 1937.

43. Lepore, M. J.: Acacia Therapy in Nephrotic Edema, Ann. Int. Med. **11**:285, 1937.

44. McMaster, P. D.: The Lymphatics and Lymph Flow in the Edematous Skin of Cardiac and Renal Disease, J. Exper. Med. **65**:373, 1937; Changes in the Cutaneous Lymphatics of Human Beings and in Lymph Flow Under Normal and Pathological Conditions, ibid. **65**:347, 1937.

the proteins that little of it could be removed by shaking with animal charcoal. When the same test was applied to plasma from patients showing massive albuminuria, it was found that the dye was loosely bound so that a large part of it could be removed by charcoal. These investigations show that this alteration in the plasma is not characteristic of amyloid disease alone but occurs in other nephropathologic conditions in which massive albuminuria and tubular degeneration occur, even in a case of severe chronic passive congestion of the kidneys. This phenomenon is looked on as primarily due to changes in the plasma proteins themselves.

Another investigation which has similar implications as to alteration of the plasma proteins is that of Kendall.[45] He finds that the familiar globulin, which is insoluble in water but soluble in dilute salt solution, is composed of two water-soluble fractions, alpha globulin and globulin x, which may be separated by a specific precipitin. Kendall finds that normal serum globulin is about 55 per cent alpha globulin and that normal serum contains 1.1 to 2.1 Gm. of alpha globulin and 0.4 to 1 Gm. of globulin x. Patients with alcoholic cirrhosis of the liver and others with chronic nephritis show alterations in the quantities and proportions of these two fractions.

Briggs [46] reports an interesting study of the formation of ammonia by the kidneys in nephrosis. By correlating data on the ratio of ammonia to excess excretion of acid and the rate of flow of urine, he finds in nephrosis evidence that the tubules tend to respond to the stimulus of acid in them by an unusually high secretion of ammonia. He believes that in nephrosis the low volume of urine, which is found in spite of normal glomerular filtration, is due to excessive resorption of threshold substances, and he believes that this may be a contributory factor in the production of nephrotic edema.

A study has been made by Keutmann and Bassett [47] of the factors which influence proteinuria. They observed simultaneous increase in the protein content of the urine and the urea clearance when the protein of the diet was increased, when diuretics were administered or when the volume of the blood plasma was increased by transfusion of plasma. They conclude that the protein content of the urine varies with

45. Kendall, F. E.: Studies on Serum Proteins: I. Identification of a Single Serum Globulin by Immunological Means; Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, J. Clin. Investigation **16**:921, 1937.

46. Briggs, A. P.: Functional Activity of Renal Epithelium in Certain Types of Nephritis as Indicated by Secretion of Ammonia, Arch. Int. Med. **60**:193 (Aug.) 1937.

47. Keutmann, E. H., and Bassett, S. H.: Studies on the Mechanism of Proteinuria, J. Clin. Investigation **16**:767, 1937.

glomerular permeability, with the rate of glomerular filtration, with the amount of new material present in the diet or in reserves of the body from which plasma proteins may be derived, and with artificial increase of the plasma protein content, such as follows transfusion.

"HEPATORENAL SYNDROME"

The term hepatorenal syndrome appears frequently in the literature. In the minds of some it connotes serous inflammatory edema of the kidney, occurring in some cases of severe hepatic injury, terminating in anuria and uremia. Nonnenbruch [48] finds that this lesion of the kidney is not invariably present. The disturbance of renal function may be of extrarenal origin. This syndrome may occur in a wide variety of states, ranging from Weil's disease to food poisoning.

Elsom [49] studied 16 patients with obstructive jaundice and 1 with arsenical hepatitis, who gave evidence of renal injury. The urine contained an excessive number of casts, epithelial cells and leukocytes. Hematuria and albuminuria were inconspicuous. The urea clearance was frequently reduced. As the jaundice subsided, evidences of renal injury disappeared.

HYPERPARATHYROIDISM IN RENAL DISEASE

Highman and Hamilton [50] have shown that there is an increased activity of the parathyroid glands in chronic renal disease, as measured by the method of Hamilton and Schwartz. This method consists of injecting the blood to be tested into rabbits and observing the degree of increase in the calcium content of the serum which ensues if parathyroid hormone is present.

After daily injection of phosphate into rabbits, hyperplasia of the parathyroid glands was observed by Drake, Albright and Castleman.[51] These experiments elucidate the method by means of which such hyperplasia may arise in chronic renal insufficiency with phosphate retention.

MISCELLANEOUS REPORTS

Bliss [52] offers an interesting explanation of the ulcerative stomatitis sometimes seen in uremic patients. He found urease present in the

48. Nonnenbruch, W.: Ueber das entzündliche Ödem der Niere und das hepatorenale Syndrome, Deutsche med. Wchnschr. **63**:7 (Jan.) 1937.

49. Elsom, K. A.: Renal Function in Obstructive Jaundice, Arch. Int. Med. **60**:1028 (Dec.) 1937.

50. Highman, W. J., Jr., and Hamilton, B.: Hyperparathyroidism in Kidney Disease, J. Clin. Investigation **16**:103, 1937.

51. Drake, T. G.; Albright, F., and Castleman, B.: Parathyroid Hyperplasia in Rabbits Produced by Parenteral Phosphate Administration, J. Clin. Investigation **16**:203, 1937.

52. Bliss, S.: Cause of Sore Mouth in Nephritis, J. Biol. Chem. **121**:425, 1937.

tartar of the teeth. When the urea content of the saliva is increased the liberation of ammonia is believed to cause the injury to the cheeks and gums adjacent to the deposits of tartar. To relieve the condition, tartar should be removed.

Gamble [53] has written a masterly study of the renal defense of extracellular fluid. He studied the water economy resulting from the fact that mixtures of urea and salt can be removed in the urine in higher concentrations than can be reached by water or salt alone. In view of the fact that sluggish production of ammonia in chronic nephritis results in a deficit of fixed base, an adequate intake of salt is required to prevent gradual dehydration.

53. Gamble, James L.: Renal Defense of Extracellular Fluid: Control of Acid Base Excretion and the Factors of Water Expenditure, Bull. Johns Hopkins Hosp. **61**:174, 1937.

Book Reviews

Food and the Principles of Dietetics. By Robert Hutchison, M.D., and V. H. Mottram, M.A. Eighth edition. Price $6.75. Pp. 634, with 32 figures and 3 colored plates. Baltimore: William Wood & Company, 1936.

This book has a proud and honorable record. Forty years ago Dr. Hutchison began giving the students of the London Hospital a course of lectures on dietetics, and so gratifying was the reception accorded these lectures that out of them grew the present volumes. The first edition appeared on this side of the water in 1901. Ever since, from time to time, reprintings and new editions have been forthcoming as often as seemed necessary. Each new edition has been much like its predecessor. The ultimate goal always has been to make the subject of dietetics interesting, alive and up-to-date; hence, each edition has been written so that it is readable, and whatever minor changes were necessary have been made in the text so as to keep the subject matter abreast of the times. The eighth edition is no exception.

The *Lancet,* in 1900, set its stamp of approval on the first edition by saying that it was to be cordially recommended as dealing most instructively with a subject which is not generally studied with the care which its importance demands: "Nowadays we are presented with all manner and kinds of foodstuffs, some undoubtedly of value but others undoubtedly worthless, and it is important that all those who are concerned with the subject of dietetics (and who are not?) should have some reliable information upon which to found an opinion."

In the United States there has seemed to be slowness in appreciating the soundness and reliability of the information contained in this book. The ARCHIVES OF INTERNAL MEDICINE, for instance, has never before reviewed it, and *The Journal of the American Medical Association* has acknowledged only the third, fifth and seventh editions. Of the latter, however, it was said (*J. A. M. A.* **101**:953 [Sept. 16] 1933), "It is a valuable textbook for students and practitioners of medicine and those desiring a general basic knowledge of foods and nutrition. All classes of common foods and the important problems of nutrition are given appropriate attention. References to important original papers are given in footnotes; the subject matter is simply and clearly presented." What was stated then applies with equal fairness now.

At this late date the ARCHIVES feels presumptuous in attempting to compliment a book so much older and more mature than itself. However, a curtsey is dropped to the eighth edition with much pleasure; this edition, like all the others, is a sane, practical and stimulating textbook for those desiring a general basic knowledge of nutrition and its problems.

Endocrinology: Clinical Application and Treatment. By August A. Werner, M.D., Assistant Professor of Internal Medicine, St. Louis University School of Medicine. Price, $8.50. Pp. 672, with 265 illustrations. Philadelphia: Lea & Febiger, 1937.

As the author suggests in his preface to this book, there is at present a great demand from the medical profession for information on treatment of endocrine conditions. He has attempted to meet this demand by supplying a volume, not too long, which deals simply with endocrinology and which, so far as possible, is devoid of frills.

The book begins with a clear account of the anatomy of the autonomic nervous system and the relation of this system to the glands of internal secretion. There follow chapters which deal with the anatomy and physiology of each of the glands individually, which describe the various clinical features that are encountered

when the function of one or more of the endocrine glands is disturbed and which discuss treatment of endocrine conditions. There are many carefully selected illustrations to illuminate the text. An excellent bibliography appears at the end.

One of the appealing characteristics of this book is that it is not overpretentious. The hard-headed clinician will enjoy it because it lays chief emphasis on what is known about endocrinology, because it hints so logically about what may be hoped for in the future from endocrinology and because it admits so often and so engagingly that in the light of the present knowledge of this or that complex, no endocrine treatment is of proved value. The student will enjoy it because it is clearly written and well assembled. On the whole it is a good book, heartily to be recommended.

Registro e interpretación de la actividad cardiovascular del lactante normal. By Angel S. Segura, M.D. Pp. 118. Buenos Aires: Talleres Gráficos Alcion, 1937.

This monograph consists of a discussion of the author's experimental studies of cardiovascular function in normal infants by objective methods. He employed the phonocardiograph, electrocardiograph, Frank capsule and other physical instruments for his observations. He made individual and simultaneous records of the heart sound, electrocardiograms and fontanellar, femoral and tibial pulsations in an attempt to observe the time relations between the various phases of the respective cardiovascular activities. The data on the heart sounds of infants led him to conclude that the third heart sound, which is frequently heard in infants, occurs between the first and the second sound and is due to auricular systole. The fontanellar, femoral and tibial pulse waves were studied not only as to time relation to various phases of cardiac activity but as to configuration and variations with respect to age. The phases of the cardiac cycle, heart rate and rhythmicity and the electrocardiogram were observed in an effort to establish a normal and to determine the presence of such correlating factors as age and sex.

Many tables and illustrations are dispersed throughout the book and increase its value. A general summary, which is given in Spanish, French, English and German, is included at the end of the dissertation. A bibliography and a brief index constitute the final pages of the monograph. Segura's presentation should prove of considerable value to those especially interested in cardiovascular physiology.

News and Comment

Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.—The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation is now in its fifteenth year. Twenty-six grants were made by this foundation during 1937, eighteen of which were to scientists outside the United States.

Applications for grants to be made during the year 1938-1939 should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, so as to reach him prior to May 1, 1938. There are no formal application blanks. Letters asking for aid should include a definite statement of the qualifications of the investigator, an accurate description of the proposed research, the size of the grant requested and the specific use of the money to be expended. It is highly desirable to include a letter of recommendation from the director of the laboratory or clinic in which the work is to be done.

The purposes for which this fund may be used have previously been mentioned in the ARCHIVES (**55**:344 [Feb.] 1935).

American Physiological Society.—The American Physiological Society will meet with the federated societies at the Lord Baltimore Hotel, Baltimore, March 31 to April 2, 1938. The program includes a consideration of the circulation, the central nervous system, gastrointestinal motility, the choroid plexus, the electrolytes and water balance, endocrinology, the heart, the nerve fibers and reflexes, bile secretion, hepatic lipids and the appetite, the special senses and general physiology, energy metabolism and anoxia. There will be a symposium on the last-mentioned subject on the final day, which will undoubtedly be of considerable interest to physiologists and physicians alike.

A special all expense, low rate tour ($41.50 and up) will leave from Chicago on Tuesday afternoon, March 29.

For further particulars address Prof. A. B. Luckhardt, the University of Chicago.

Association of American Physicians.—The annual meeting of the Association of American Physicians will be held in Atlantic City, N. J., May 3 to 5, 1938.

Correspondence

FOUR LEAD ELECTROCARDIOGRAM

To the Editor:—In view of the recent recommendations of the special committee of the American Heart Association on chest leads (Standardization of Precordial Leads, J. A. M. A. **110**:395 [Jan. 29] 1938; Standardization of Precordial Leads; Supplementary Report, ibid. **110**:681 [Feb. 26] 1938), it seems worth while to revise figure 15 and table 6 which accompanied our recent article on the four lead electrocardiogram (Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, Arch. Int. Med. **61**:241 [Feb.] 1938) so that they will conform with the recommendations submitted by this committee for standardizing chest leads.

We have been accustomed to taking chest leads at Michael Reese Hospital with the chest electrode in the fourth intercostal space and in the left parasternal line and with the indifferent electrode on the left leg, the connections being arranged so that relative negativity of the precordial electrode causes an upright deflection; in our communications this has been called lead IV. The committee's first report recommended the reversal of the electrodes so that relative positivity of the chest electrode causes an upright deflection. In their second report the lead employing the location of the chest electrode which we have used is designated CF_2. Accordingly, we have revised figure 15 so as to make the following changes: (*a*) we have called the lead IV which we have been accustomed to use lead IV—old, (*b*) we have put a plus and a minus sign on the electrocardiogram in stage 1 (normal contour) to designate the direction the deflections would take when the chest electrode became relatively positive and relatively negative with respect to the leg electrode and (*c*) we have added a new column, which we call lead IV—new (CF_2) to show the appearance of the electrocardiogram with the chest electrode in the position we have employed but with the chest and indifferent electrodes arranged as recommended by the special committee. It will be seen to be a mirror image of lead IV—old. Relative positivity and negativity of the chest electrode with respect to the leg electrode is shown in this column by a plus or a minus sign as in the preceding column.

In this way the reader can correlate the old and the new way of taking chest leads and can obtain the sequential diagrammatic picture of typical anterior and typical posterior infarction when using the old technic and the new technic for taking chest leads. This, we believe, should also serve the useful function of simplifying the transition from the old to the new style of chest leads for cardiologists who have been using the old style. We believe, on the basis of unpublished results, that the appearance of the chest lead will not be materially different when the chest electrode is placed over the apex (IV_F) or in the positions labeled by the committee CF_2, CF_4, CF_5. (We are still not in favor of the apex position, for reasons enumerated in our communication.)

In table 6 we have changed the column dealing with the direction of the deflections in lead IV so that it now expresses the direction of the deflection in this lead in terms of the relative potential of the chest electrode with respect to the leg electrode. Thus this table can now be used with either the old or the new technic.

TABLE 6 (revised).—*Classification of Types of Coronary Insufficiency*

Type of Myocardial Involvement			Type of Coronary Involvement	Location of Myocardial Involvement	Most Common Type of Electrocardiographic Change*		Cases Which Illustrate the Type
I. Subacute	Definite myocardial infarction	A. Uncomplicated or classic forms	Thrombotic occlusion	Anterior infarction	ST_1 + T_1 —	QRS_4 — ST_4 + T_4 — or ±	8 cases (fig. 1)
				Posterior infarction	ST_3 + T_3 —	QRS_4 ± ST_4 — T_4 ++	3 cases (fig. 4*A* to *C*)
			Sclerotic occlusion	Anterior infarction	ST_1 — T_1 —	QRS_4 — T_4 ±	7 cases (figs. 2 and 3)
				Posterior infarction	T_3 —	QRS_4 — or ±	1 case (fig. 4*D*)
		B. Complicated or atypical forms		Old posterior with recent anterior infarction	Often like anterior infarction		4 cases (figs. 5, 7*A* and *B* and 11*A*)
			Both arteries occluded	Old anterior with recent posterior infarction	Often like posterior infarction		4 cases (figs. 6*A* and *B*, 7*C* and 11*B*)
			No complete occlusion	Multiple small infarcts	Atypical		2 cases (fig. 8*A* and *B*)
II. Chronic, progressive or nonprogressive	Fibrosis without infarction		Advanced coronary sclerosis	No infarct visible; fibrosis usual	1. Like anterior infarction 2. Like posterior infarction 3. Indeterminate		2 cases (fig. 10*A* and *B*) 5 cases (fig. 9)
III. Acute, transitory	Transitory ischemia		Indeterminate	Indeterminate	ST and T deviations variable		2 cases (figs. 8*C* and 10*C*)

* Inferior number 4 applies to lead CF_2 described in the report of the special committee of the American Heart Association (Standardization of Precordial Leads: Supplementary Report, J. A. M. A. **110**: 681 [Feb. 26] 1938). + or — in this lead indicates the relative potential of the chest electrode with respect to the leg electrode.

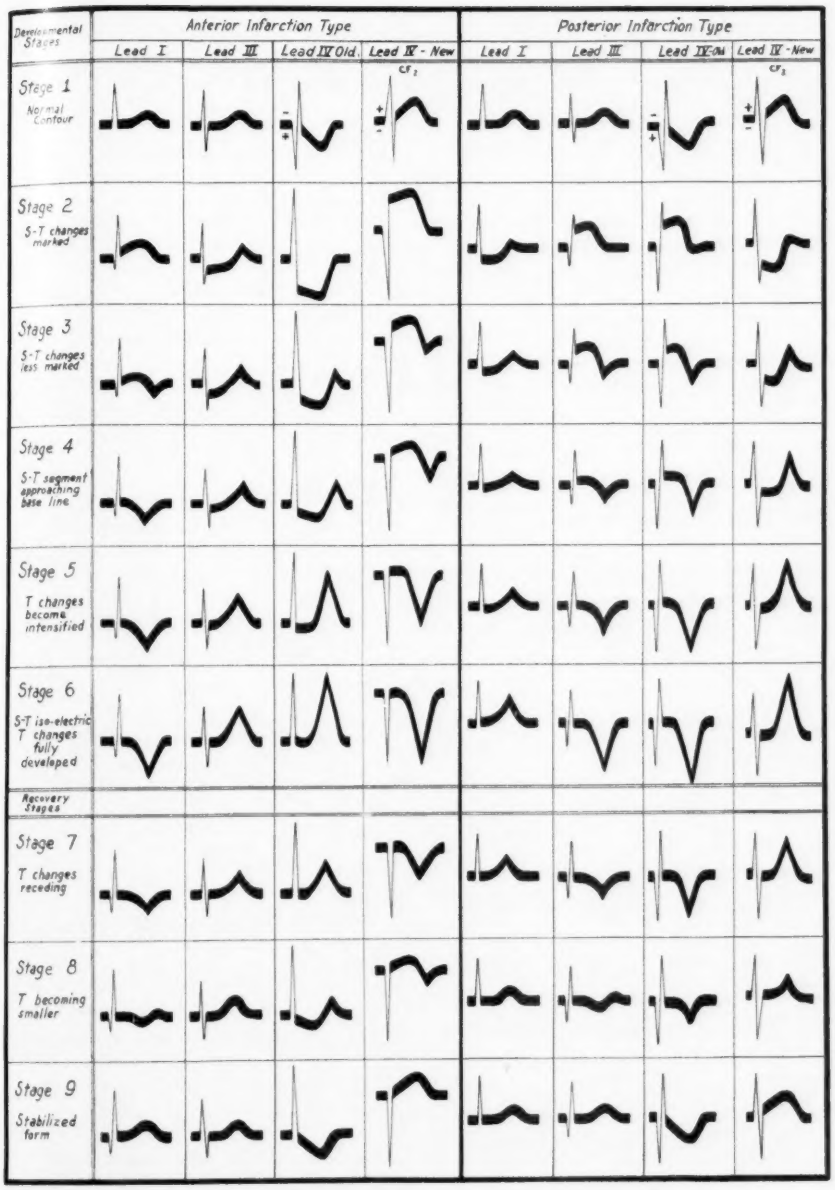


Fig. 15 (revised).—Diagrammatic illustration of the classic type of changes usually found in leads I, III and IV in the stages of development of and recovery from uncomplicated infarctions of the anterior and of the posterior wall due to sudden thrombotic closures. In each instance the appearance of lead IV, as we have been taking it heretofore, is shown side by side with the new lead IV—in reality, lead CF_2, according to the recent report of the special committee of the American Heart Association published in *The Journal of the American Medical Association* (Standardization of Precordial Leads; Supplementary Report, J. A. M. A. **110**:681 [Feb. 26] 1938). In lead IV + and — refer to the relative potential of the precordial electrode with respect to the leg electrode.

We regret that our report was in the process of publication during the time that the special committee of the American Heart Association was considering the standards to be employed for chest leads so that we could not revise our illustrations and data to conform with their report. The present communication should rectify this situation as far as this particular diagram and table are concerned. As regards the other illustrations in our previous reports for which the old technic was used, we recommend that the reader place a mirror above each figure and look at the image in the mirror to obtain the contour of the electrocardiogram which would have been obtained if the recommendations of the special committee had been followed. As regards the text, the reader will need to make the following substitutions: negative for positive, down for up, depressed for elevated, inverted for upright and below the iso-electric line for above the iso-electric line and vice versa in order to revise the text to conform with the recommendations of the special committee.

A. Bohning, M.D., Chicago.
Louis N. Katz, M.D., Chicago.